مستشفى الملك فيصل التخصصي ومركز الأبحاث
King Faisal Specialist Hospital & Research Centre
Gen. Org. مؤسسة عامة

KFSH&RC

RESEARCH REPORT

2015

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KFSH&RC

RESEARCH REPORT

2015

Our mission is to be a centre of excellence in biomedical research.

We are dedicated to the advancement of science and the translation of research findings into better healthcare.

We strive to provide an environment that enhances individual growth, collaboration, achievement and recognition.

Qasim Al Qasabi, MD, FRCSI, FACS
Chief Executive Officer

The King Faisal Specialist Hospital and Research Centre (Gen. Org.) continues to meet and overcome the constant challenge to deliver world class services in an ever changing environment. With healthcare demands growing in terms of both volume and complexity, innovative research is a core competency of leading institutions and is essential for delivery of better care to our patients now and in the years to come. I have every confidence that given the dedication and high caliber of our staff, the General Organization will continue to deliver premium care to the people of Saudi Arabia.

Reviewing the past decade of research activities, it is encouraging that the General Organization's publications cover numerous medical disciplines with significant emphasis on the strategic areas of oncology, cardiovascular disease, neurology, genetics and transplantation. The quality of research undertaken is recognized globally and features on the covers of some of the world's leading journals. Additionally, the General Organization's citation index is comparable to many leading countries in the field of basic and translational research. Over the last ten (10) years, publications involving researchers from the General Organization exceeded 3,500 articles with an impressive impact of almost 30,000 citations. Also, there are more than 20 patents filed with at least ten (10) issued patents. These figures are highly commendable and are a significant contribution to global biomedical knowledge.

One of the priorities in the approved Strategic Plan (Vision 2020) is research development and by investing in genetic medicine and bioinformatics, the path to Personalized Medicine is well underway. Our clinical and basic research efforts are focused on identifying novel disease mechanisms and translating these findings into improved patient care and outcomes in the areas of Oncology, Genetics, Cardiology, Neurosciences and Transplantation.

As a leading healthcare provider our success is firmly bound to an active and strong research program. The Executive Management team take great pride in the achievements of the Research Centre and fully support research dedicated to more efficient healthcare and better patient outcomes.

Sultan T. Al-Sedairy, PhD
Executive Director,
Research Centre

As a leading regional and international healthcare facility we are often called upon to address immediate, near and long term issues relating to health and disease of our patients or the community at large. Effectively addressing viral outbreaks such as MERS, chronic diseases such as diabetes and cardiovascular disease or the rapidly changing fields of oncology, genetics and transplantation can only be achieved through engagement in relevant basic, clinical and translational research. In keeping with these requirements, research undertaken by KFSH&RC is dedicated towards improving health in the Saudi population, maintaining international levels of healthcare and in some areas leading the way.

During 2015 programs within the Research Centre continued to expand our capacity in the areas of cell biology, transplantation, oncology, infectious diseases, genomics and bioinformatics. Our research has highlighted ethnic and geographical differences in the aetiology of disease and the effectiveness of therapies. Engagement in epidemiological studies, infectious diseases research, biomarker discovery, stem cell therapies, genomics, proteomics and investigation of the biological basis for common disease, within the Saudi population and Arab peninsula, are positioning us for the future involving targeted therapies and personalized medicine. In addition to original research studies extensive service work is undertaken by the Research Centre to facilitate transfer of the most current technologies for treatment, screening and diagnosis, leading to better patient care and the prevention of disease.

KFSH&RC is clearly a regional and international leader in many fields of research as attested by our publication record, citation index, innovation and collaboration. Expansion of our activities are challenging in the current environment. However, I remain confident that we can consistently improve the quality of our research through increased participation and dedication among the many healthcare professionals in our institution. Research and innovation remain at the core of being a world-leading healthcare institution.

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RESEARCH CENTRE

BIOSTATISTICS, EPIDEMIOLOGY AND SCIENTIFIC COMPUTING

BIOSTATISTICS SECTION

HEAD

Edward B. De Vol, PhD

MEMBERS

Saleh Al-Ageel

Samia Al-Hashim

Abdelmoneim Eldali

Parvez Siddiqui

RESEARCH ACTIVITIES

PROJECT TITLE: Thromboembolic Disorders Registry
RAC# 2001 045, BESC# 20010004A

PRINCIPAL INVESTIGATOR: *Sheikh A*

PROJECT DESCRIPTION: The Thromboembolic Disorders (TED) Registry of King Faisal Specialist Hospital and Research Center was established in February 2001 as collaboration between Registries Core Facility of Biostatistics, Epidemiology and Scientific Computing Department and King Faisal Internal Medicine Department. Objectives: 1. Data resource that could assist the health care to evaluate the results of their therapeutic effort and analyze reasons for complication like the Thromboembolic episodes or Bleeding disorders occurring during Anticoagulation Therapy. 2. To provide leadership in establishing and maintaining comprehensive TED Registry in collaboration with other National Organization. 3. Serve as database for future research. 4. Data resource could enable us to improve some methods of prophylaxis of DVT and standardize the recommended regimens for prophylaxis, which could lead to improvement of the approaches to prevention. 5. Enable stratification of patients into different risk groups.

PROGRESS: Both data analysis and presentation for this project have been done in SAS for the purpose of generating the TEDR Annual/Cumulative Report.

PROJECT TITLE: Cleft Lip/Palate and Craniofacial Anomalies Registry
RAC# 991 030, BESC# 19990007A

INVESTIGATORS: *Al Johar A, Al Shail E, Al Rubaiya A, Al Jarba E, Hashim S*

PROJECT DESCRIPTION: The Cleft Lip and Palate (CLP) registry was established in 1999. The purpose of this study is to provide a database on cleft lip/cleft palate patients at KFSH&RC. CLP are one of the most common human malformations and the most common malformation of the face. CLP is a complex and chronic disability lasting from birth through adulthood. The objective of this study is to determine the type and prevalence of CLP in the KFSH&RC population. In addition, the data will contribute information for reporting, conducting research studies and health care planning.

PROGRESS: Both data analysis and presentation for this project have been done in SAS for the purpose of generating the CLPR Annual/Cumulative Report.

PROJECT TITLE: Epilepsy Registry
RAC# 2011 059, BESC# 19970009A

PRINCIPAL INVESTIGATOR: *Al Semari A*

PROJECT DESCRIPTION: At the end of 1998, a Comprehensive Epilepsy Program was established at King Faisal Specialist Hospital and Research Centre (KFSH&RC). The main goals of the program are to treat referred patients medically and to disseminate accurate information on epilepsy to concerned persons throughout the Kingdom. The Department of Neurosciences (NS) and Biostatistics, Epidemiology and Scientific Computing (BESC) have established a KFSH&RC-based Registry. This will provide data from which to assess the magnitude of the disease, to determine the pattern of epilepsy and its commonly related factors, and to provide descriptive statistics and documentation of treatment procedures and outcome in epileptic patients. It will also enable study of medical, psychological, social and demographic factors, and their effect on society. It is hoped it will serve as a model for the establishment of a Kingdom-wide registry for this disease.

PROGRESS: Both data analysis and presentation for this project have been done in SAS for the purpose of generating the Epilepsy Registry Annual/Cumulative Report and for paper/poster presentation and publication.

PROJECT TITLE: Congenital Heart Disease Registry
RAC# 991 026, BESC# 20080011A

INVESTIGATORS: *Al Mohanna F, Shoukri M, Canver C, Al Yousef S, Momenah T, Joufan M, Al Halees Z, Omrani A, Subhani S, Al Firm A, Dessouky N, Bawayn N, Barhoush L, Khalil H, Marzouky M, Al Zahrani A, Hashim S*

PROJECT DESCRIPTION: Congenital heart defect (CHD) is an inborn anomaly due to unknown causes and is an important cause of infant mortality and morbidity. CHD is defined as a gross structural abnormality of the heart, great vessels or the conduction system that is actually or potentially of functional importance. Studies of the incidence of this disease in populations provide different incidence rates. The congenital heart defects registry of the King Faisal Specialist Hospital and Research Centre (KFSH&RC) started in 1998 as a collaboration between the Registries Core Facility of the Biostatistics, Epidemiology and Scientific Computing Department and the King Faisal Heart Institute. All patients presenting to the hospital with congenital heart disease are registered. It is designed for the collection, processing, management, and analysis of data on CHD patients. Pilot testing of the Case Report Form (CRF) was conducted from October 1997 to December 1997 to conform the viability of the data abstraction/collection. It is noteworthy to mention that the registry is internet-based (web-based), facilitating expansion efforts to other institutions in the Kingdom.

PROGRESS: Both data analysis and presentation for this project have been done in SAS for the purpose of generating the CHDR Annual/Cumulative Report and for paper/poster presentation/publication.

PROJECT TITLE: Primary Immunodeficiency Disease Registry
RAC# 2081 111, BESC# 20080729E

INVESTIGATORS: *Al Saud B, Al Muhsen S, Baig M, Afzal J, Hashim S*

PROJECT DESCRIPTION: Primary Immunodeficiency Disorders (PID) are a heterogeneous group of diseases that predispose patients to recurrent infection, autoimmune disease, and malignancy. There are 150 different phenotypes of PID; in most cases a genetic defect is identified. PID registries from countries around the world have shown wide geographical and racial variations in the prevalence and pattern of PID. These registries helped in determining the frequency and the natural history of PID in these countries. Moreover, a registry can significantly improve research in the field of PID by collecting data over time and by connecting centers nationally and internationally even. The rationale is to determine the magnitude of disease and types of PID disease encountered in our population at King Faisal Specialist Hospital and Research Centre (KFSH&RC). Upon successful data collection, other health care centers in Riyadh and subsequently across the country will be added to have national representation of the registry. The PID registry will be a retrospective and prospective ongoing hospital-based registry of all patients diagnosed with any of the PID diseases that meet the criteria of diagnosis by the World Health Organization. Data capture form will be developed and filled by chart review or personal interview of patients. Software will be designed for data entry. Microsoft SQL Server will be used to develop and administer the database, which could be accessed using a standard web browser. Data analysis will be handled by the Biostatistics, Epidemiology, and Scientific Computing Department at KFSH&RC.

PROGRESS: Both data/statistical analysis and presentation for this project have been done in SAS for the purpose of generating the PIDR Annual/Cumulative Report and for paper/poster presentation/publication.

PROJECT TITLE: Neural Tube Defects Registry
RAC# 991 029, BESC# 19990018A

INVESTIGATORS: *Al Shail E, Shoukri M, Yassen I, Subhani S, Al Abdulaaly A, Al Zayed Z, Kattan H, Kurdi W, Sakati N, Hashim S*

PROJECT DESCRIPTION: Neural Tube Defects (NTD) are serious birth defects with symptoms that range from mild to severe degrees. They are a group of birth defects, which have a common origin in failure of the neural tube to develop properly during the embryonic stage. The King Faisal Hospital and Research Center Neural Tube Defects Registry was established in March 2000 through the joint efforts of the departments of Neurosciences and Biostatistics, Epidemiology and Scientific Computing (BESC), Pediatrics, Orthopedics, Urology, and Obstetrics and Gynecology. The registry is designed for the collection, management and analysis of data belonging to patients with NTD. The NTD registry is located within the BESC department at King Faisal Specialist Hospital and Research Centre. The registry conducts active surveillance to identify information about NTDs for patients residing all over the Kingdom.

PROGRESS: Both data/statistical analysis and presentation for this project have been done in SAS for the purpose of generating the NTDR Annual/Cumulative Report and for paper/poster presentation/publication.

PROJECT TITLE: First Study of Pattern of Epinephrine Auto Injector Prescription for Anaphylaxis in a Large Tertiary Care Hospital in Saudi Arabia
RAC# 2121 057, BESC# 20130724A

INVESTIGATORS: *Sheikh F, Amin R, Khaliq A, Al Otaibi T, Al Gazlan S, De Vol E, Hashim S*

PROJECT DESCRIPTION: Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. Anaphylactic reactions can be triggered by allergic responses to a wide range of substances including food, medications, wasp or bee stings, and latex. Anaphylaxis has a reported mortality of 1–2% in the USA. The rate of occurrence is increasing in industrialized countries. The incidence and prevalence in the KSA is unknown.

Prompt assessment and treatment are critical in anaphylaxis, as respiratory or cardiac arrest and death can occur within minutes. Prompt intramuscular injection of epinephrine is one of the cornerstones of treatment of Anaphylaxis. It is therefore important to study the dispensing pattern of Epinephrine in our region. This will help us understand the epidemiology of Anaphylaxis and aid ongoing efforts to reduce morbidity and mortality from anaphylaxis and could provide important clues for primary prevention.

PROGRESS: Data collection, validation, analysis, and presentation for this project have been done in SAS for the purpose of paper publication/ presentation.

PROJECT TITLE: Prevalence of Depression in Cancer Patients in KFSH&RC-Riyadh
RAC# 2121 146, BESC# 20131111A

INVESTIGATORS: *Al Hakami H, Al Sayed A, Al Masaad S, Al Harbi N, De Vol E, Hashim S*

PROJECT DESCRIPTION: Oncologic diseases currently have a high prevalence and present as one of the leading causes of death in the western world. Clinical depression and emotional distress are often the outcome of the threat these diseases present to individual existence. Depression is

commonly encountered among cancer patients and has been linked with grave consequences if not promptly treated. Depression is a major public health problem and a leading predictor of functional disability and mortality. The annual economic consequences of depression have been estimated at 83 billion dollars in the United States and 118 billion euros in Europe. Optimal depression treatment improves outcomes for most patients. Although most adults with clinically significant depression never see a mental health professional, they often see a primary care physician. Yet substantial numbers of depressed primary care patients remain undiagnosed or under-treated, reflecting attitudes and practices of physicians, patients, families, and health care systems. A systematic review of 36 studies found that non-psychiatric physicians missed the diagnosis of depression in over one half of patients seen, although these findings should be interpreted with recognition of the difference between primary care and psychiatric practice in the severity of depression, the complexity of diagnosing and treating depression in the context of other chronic medical illness, and the primary care approach to diagnosis over several office visits. This topic will focus on the clinical features and diagnosis of depression. The epidemiology, pathogenesis, treatment, and prognosis of depression are discussed separately.

PROGRESS: Data collection, validation, analysis, and presentation for this project have been done in SAS for the purpose of paper publication.

PROJECT TITLE: Retrospective Analysis of Patients Profile Having Intravascular Hemolysis with Prosthetic Heart Valves: Experience at KFSH&RC

RAC# 2111 109, BESC# 20131117A

INVESTIGATORS: *Akhtar N, Ali Z, Al Emadi B, De Vol E, Hashim S*

PROJECT DESCRIPTION: Sub-clinical mild intravascular hemolysis is not an uncommon phenomenon in most patients with even normal mechanical or biological heart valves. Primary mechanism is thought to be shear stress and trauma to red blood cells (RBCs) due to abnormal turbulent flow jets. Decompensated hemolytic anemia is rare. The severity is related to type, position and especially to malfunction of the valve in the form of paravalve leak. The degree of hemolysis is not proportional to severity of valve regurgitation. The irregularity of the leaking site and the colliding angle may play an important role. An eccentric rather than central jet may cause more hemolysis. Size of the valve has not shown to be related to the degree of hemolysis. Structural deterioration as well as paravalvular leak of biological valve also may lead to intravascular hemolysis. With newer generations of the valves the incidence has decreased but not completely eliminated. Little is known about the frequency, causes and outcome of hemolytic anemia in patients with mechanical heart valves, in a diverse population of patients at King Faisal Specialist Hospital & Research Centre (KFSH&RC) Riyadh. The Heart Centre patients had been implanted with a variety of mechanical and biological valves since it became functional. We plan to review the medical records of Heart Centre's adult patient population who underwent surgery for heart valves in the form of replacement or repair and later developed hemolytic anemia; to find out the frequency, causes, treatment and their outcome. Additionally we shall look into the demographic characteristics and relative frequencies of clinical presenting features of the patients.

PROGRESS: Data collection, validation, and analysis is in progress.

SERVICES

In 2015, the Section has performed over 250 Data Clinics (computational statistics/genomic analysis) and Consultation services. The services provided include, but not limited to:

DATA CLINICS AND CONSULTATION SERVICES

Statistical consultation and data clinic services offered for scientists, clinicians, residents, fellows and administration.

- Biostatistical services (hypothesis formulation, study design, power and sample size determination, survival analysis, data analysis and interpretation),
- Statistical Genetics and Genomics (microarray analysis, genomics, transcriptomic data analysis, pathway analysis, functional, and network analyses, next-generation sequencing analysis and others),
- Methodological advice, grant application (statistical plan/write-up/grant section), and publication (analysis, re-analysis, review).
- Work on establishing a SAS Users Group (SUG) and becoming a SAS site representative in KFSH&RC

THE LIST OF OUR CLIENTS INCLUDES BUT NOT LIMITED TO:

- Oncology, Surgery, Orthopedics, - Research Centre (Genetics, Infections and immunity molecular oncology, stem cell, cardiovascular research program, and others), Medical genetics, Internal Medicine, Radiology, Neurosciences, Obs/Gyne, Medicine, Heart Institute, Pediatrics, Emergency Medicine, Health Education, Pharmacy, Physical Therapy, Kidney Transplant, Lung Transplant, Nursing, Colorectal Surgery, Family Medicine, Dental, Microbiology, HRM M&PD, NICU, CSICU, Gulf Cancer Center, National Biotechnology Center, and others

The Biostatistics Sections contributed significantly to statistical analysis and data management of the following registries and projects and helped in the preparation of the annual/cumulative report:

- Thromboembolic Disorders Registry
- Cleft Lip/Palate and Craniofacial Anomalies Registry
- Epilepsy Registry
- Neuromuscular Disease Registry
- Congenital Heart Disease Registry
- Primary Immunodeficiency Disease Registry
- Neural Tube Defects Registry
- Saudi National Mental Health Survey

TEACHING AND TRAINING

Teaching and Training activities in statistical computing and in the use of statistical software packages to improve the statistical knowledge among clinicians, scientist, postgraduate students, fellows and MS/PHD students. The following courses/training offered in 2015:

- Business Mathematics course for Medical Secretaries Program.
- Business Mathematics course for CSSD Program.

EPIDEMIOLOGY SECTION

HEAD

Yasmin Altwaijri

MEMBERS

Alanoud Bin Khuthaila, MPH
Liza Bilal
Abdulrahman Bin Muammar
Nada Bawyan
Hala Al-Assiry
Hala Khalil
Maha Al Eid
Noha Al-Tanani
Fatima Ibrahim
Sanaa Hyder
Mohammed Talal Naseemudin
Sohail Bilal

RAC APPROVED PROJECTS

PROJECT TITLE: The Saudi National Mental Health Survey: Health and Stress
RAC# 2091 093

SOURCE OF FUNDING: *SABIC, King Abdulaziz City for Science and Technology (KACST), Abraaj Capital, Ministry of Health (MOH), and King Saud University (KSU)*

OVERVIEW/AIMS: Mental Health Disorders are a major public health problem worldwide, affecting people of all ages, cultures and socio-economic statuses. It is estimated that 450 million people globally have mental disorders. The concern about the disparity between mental health service demand and supply led the World Health Organization (WHO) to start the World Mental Health (WMH) Survey Initiative in collaboration with Harvard University. The WMH has been conducted in over 30 countries to identify the prevalence, risk factors, prognosis and treatment outcome of mental disorders. Saudi Arabia launched the Saudi National Mental Health Survey (SNMHS) in accordance with the WMH Survey. The objective of the study is to estimate the psychiatric morbidity in different regions in Saudi Arabia and magnitude of disability caused by it. The SNMHS is a population-based, epidemiological survey which is administered to a nationally representative sample of Saudis living in urban and rural areas. We aim to achieve a sample of 5,000 participants; males and females above the age of 15, selected randomly from each household. This sample will cover 13 regions in the Kingdom. A face-to-face interview is conducted in the homes of the participants by WMH certified teams. The interviewing method is gender specific. During the interview, the Composite International Diagnostic Interview (CIDI 3.0), developed by Harvard University, is administered. A team of Saudi physicians and translators forming an expert panel adapted this instrument for the Saudi population. This study is important in providing vision for clinicians and health policy makers to establish relevant preventive, therapeutic, and rehabilitation services in the Kingdom.

TRAINING SESSIONS: The SNHSS team successfully conducted and concluded extensive two-week CIDI interviewer's training sessions to prepare new batches of interviewers before launching them in the regions of fieldwork, i.e. Eastern Province, Makkah, Madinah, Taif and Al-Jouf. In January, August and November of 2015 respectively, extensive training courses were held for new cohorts of interviewers for fieldwork in the Western and Northern Regions (conducted at Al Amal, Jeddah and King Faisal Specialist Hospital & Research Center, Riyadh). A booster training sessions lasting 3 days was also conducted for the travel team (i.e. field staff that travels to remote/various regions within KSA) in Taif after the Ramadan break, in August, 2015. These sessions addressed how interviewers could best tackle problematic fieldwork issues, alongside refreshing their memory on topics already covered in the main training sessions. Overall, the project has trained over 150 field staff members to-date.

DATA COLLECTION: The project has successfully completed fieldwork in 3 regions: Central, Eastern and Western. By December 2015, we also began fieldwork in one of the administrative areas in the Northern region i.e. Al-Jouf, covering Skaka, Tabarjal and Algrayat areas. While in 2014, the target for the Riyadh and Qassim administrative areas was achieved (1,152 completed interviews). In 2015, the targets for the Eastern Province (518 completed interviews) and the Makkah and Madinah administrative areas (1,166 completed interviews) were achieved. Overall, the project now has over 3,000 completed interviews (including interviews from Al-Jouf). Results of the

fieldwork will be compiled next year during the evaluation phase, along with the analyses of data from other regions of KSA.

QUALITY CONTROL: In the past, the project received recognition from the University of Michigan for exceptionally implementing quality control procedures and exceeding international quality control thresholds. We have continued to implement rigorous quality control for all the methods carried out in 2015 as well. The project is still carrying out more verifications (i.e. calling back respondents to confirm a sample of their answers and checking for interviewer cheating) than the average required amount. In this manner, the SNMHS continues to improve its quality control procedures.

RECRUITMENT: The SNMHS team continues to independently recruit new field staff for its fieldwork, which was for Western and Northern Regions in 2015. So far, we have certified a field team of over 30 interviewers to use CIDI and collect data for the SNMHS.

CONFERENCES: The principal investigator, Dr. Yasmin Altwaijri and the project manager attended the 2015 WAPOR Regional Conference in Doha, held from March 7th to 9th, 2015. Dr. Altwaijri presented the Pilot Study experience of the Saudi National Mental Health Survey. She also attended the Annual Scientific Meeting of the Harvard WHO Mental Health Consortium held in July, 2015. There, she presented updates on the progress of the Saudi National Mental Health Survey, which was well received by the participating scientists from different countries.

GENETICS AND SCIENTIFIC ADVANCEMENT: The SNMHS is one of the distinctively scientific studies participating in the WMH Survey Consortium, which continues to collect saliva samples from its respondents after obtaining an additional consent from them. The DNA specimens extracted from these saliva samples will be used to study genetic risk factors for mental health conditions prevalent in the Saudi population. So far in fieldwork, the project has successfully amassed such samples and related findings will be available in the future.

PROFESSIONAL DEVELOPMENT: Dr. Zeina Mneimneh, Assistant Research Scientist at the Survey Research Center (SRC), Institute for Social Research, University of Michigan visited the SNMHS central office in KFSH&RC, Riyadh and conducted workshops on survey research methodology (total survey error framework and sample error) for the SNMHS team in February, 2015. The survey also collaborated with the Biostatistics, Epidemiology and Scientific Computing Department at KFSH&RC to conduct Statistical Analysis System (SAS) workshops and by January 2015, the project had a newly certified SAS user, who since then has also been remotely taking data management courses given by the Survey Research Center (SRC) at University of Michigan.

LIST OF PEER-REVIEWED PUBLICATIONS

- Koenig, H. G., Al Zaben, F., Sehlo, M. G., Khalifa, D. A., Al Ahwal, M. S., Qureshi, N. A., & Al-Habeeb, A. A. (2014). Mental Health Care in Saudi Arabia: Past, Present and Future. Open Journal of Psychiatry, 4(02), 113.

PROJECT TITLE: Preventive Health Care among Elderly Women

RAC# 2121 020

OVERVIEW/AIMS: Saudi Arabia like most countries in the world is facing the challenge of an ageing population. Increase in elderly population will have an impact on health care and social services. Geriatric medicine will be a large part of every

physician's practice. Across the industrialized world, women still live 5 to 10 years longer than men. Among people over 100 years old, 85% are women. Lifestyle modifications, screenings, early identification, and appropriate intervention may prevent many chronic conditions that cause morbidity and mortality in elderly women. There is a need to improve delivery of preventive health care to older women.

OBJECTIVES: To describe the current clinical practice of preventive health services (screening, counselling and immunization) among elderly women in outpatients' clinics (internal medicine clinics and medical polyclinics) at KFSH&RC. We plan to compare the preventive health measures including screening tests, immunizations, and counselling among women aged 80 and older and women aged 65 to 79.

This study can help physicians to improve their clinical practice about preventive health care of elderly women. Up to our knowledge this is the first study of preventive health services among elderly women in Saudi Arabia.

ACHIEVEMENTS: Data collection completed. Statistical analysis underway.

PROJECT TITLE: Anticoagulation of Behcet's Disease with Thrombosis: A Series of 36 Cases in a Tertiary Care Centre in Saudi Arabia
RAC# 2151 126

OVERVIEW/AIMS: Behcet's disease (BD) is a chronic relapsing multisystem inflammatory disorder of unknown etiology. It was first described in three patients with a triple symptom complex of aphthae, genital ulcers, and hypopyon uveitis in 1937 by Hulusi Behçet. BD is characterized by a range of clinical features that include oral and genital ulceration, variable skin lesions, ocular involvement, arthritis, vasculitis, and central nervous system and gastrointestinal manifestations. Although found worldwide, BD is most prevalent along the Silk Road, stretching from the eastern Mediterranean through the Middle East to the East Asia rim, with the highest prevalence is in Turkey (400 cases/100,000 persons). There are no specific symptoms, signs nor laboratory findings in BD. The diagnosis is made by recognizing a group of clinical features. Hence various experts have developed various clinical criteria. The Diagnostic Criteria defined by the 1990 International Study Group (ISG) for BD remain the most widely used among the experts. This study is a descriptive retrospective chart review of 34 patients of Behcet's disease with thrombosis on long term anticoagulation. In this study, we will report the main characteristics, treatment, and long-term outcomes of Behcet's disease with thrombosis on anticoagulation.

ACHIEVEMENTS: Data collection completed. Statistical analysis underway.

PROJECT TITLE: The Demographic Characteristics and Risk Factors of Dementia in an Elderly Population in Saudi Arabia
RAC# 2151 126

OVERVIEW/AIMS: Dementia is a disorder that is characterized by loss of global cognitive ability in a previously unimpaired person, beyond what might be expected from normal aging. Although a number of definitions exist for dementia, the DSM-IV- Text Revised definition is widely accepted and includes the following (1): Evidence from the history and mental status examination that indicates major impairment in learning and memory as well as at least one of the following: Impairment in handling complex tasks, impairment in reasoning ability, impaired spatial ability and orientation and impaired language.

The major dementia syndromes include: Alzheimer disease (AD), Dementia with Lewy bodies (DLB),Frontotemporal dementia (FTD), Vascular (multi-infarct) dementia (VaD) and Parkinson disease with dementia (PDD). Dementia can be accurately diagnosed through clinical evaluation, cognitive tests, basic laboratory evaluation and structural imaging.

The population in Saudi Arabia is getting older. According to the last Saudi census the life expectancy at birth is 74 in 2011 and expected to be 77 in 2025. The number of elderly aged 65 years and over rose in absolute numbers from 401,861 in 1992 to 609,573 in 2007 (5). Increased in elderly population will have an impact on health care and social services. The cost of caring for one person with this disorder at home or in a nursing home is more than $47,000 per year in USA

There is a little information about dementia in Saudis. We have scanty data regarding the demographics characterizing this population or the etiologic diagnoses among those affected in Saudi Arabia (7). Early impairments of cognitive function in Saudis are rarely diagnosed, most of patients presentation are in the late stage of the disease, due to lack trained physicians in dementia. The use of cognitive screening in the routine evaluation of elderly people with cognitive problems is not a general rule in the medical practice.

The prevalence of diabetes, hypertension, high cholesterol and smoking are high in Saudis (8,9,10,11). These are well known risk factors for dementia which can be prevented.

The underlying message of this study is to aware the public and health system about the impact of dementia in Saudis and the need for trained physicians for early diagnosis.

OBJECTIVES

1. Describe the demographic characteristics and the risk factors of dementia in an elderly population in Saudi Arabia at a tertiary care hospital
2. Find out the prevalence and severity of different types of dementia
3. Describe the current clinical practice of dementia
4. Estimate survival after a diagnosis of dementia

ACHIEVEMENTS: Data collection completed. Data entry began.

CLINICAL TRIALS AND REGISTRIES

HEAD

Bader Al-Hablani

MEMBERS

Amani Al-Meharish
Maram Al-Tuwaijri
Dhefaf Al-Abdaly
Sara Al-Kaf
Nadia Dessouky, MD

RESEARCH ACTIVITIES

PROJECT TITLE: Prospective Observational Chart Review to Assess Health Resource Utilization and Pattern of Care Associated with Skeletal Related Events (SRE) in Patients with Bone Metastases Secondary to Solid Tumors at KFSH&RC
RAC# 2151089

PRINCIPAL INVESTIGATOR: *Shouki Bazarbashi, MD, Medical Oncology- KFSH&RC- Riyadh*

PRIMARY OBJECTIVE: To estimate health resource utilization (HRU) and financial cost associated with SREs in solid tumors

SECONDARY OBJECTIVES:

- To describe patterns of bone modifying agents (BMA) use (e.g., types of agents, length of therapy, frequency of dosing) in subjects with bone metastases secondary to solid tumors
- To correlate pattern of use of BMA with the development of subsequent SRE's
- To evaluate the cost of SRE vs the cost of BMA using frequencies in published international data and local cost data obtained from this study

CURRENT STATUS: Planned to start during February 2016.

PROJECT TITLE: Bi-weekly Cetuximab and XELIRI(Capecitabine and Irinotecan) as First Line Therapy in K/N-RAS Wild Type Advanced Colorectal Cancer: Phase I-II CETUXIRI Study
RAC# 2151062

PRINCIPAL INVESTIGATOR: *Ahmad Al-Zahrani, MD, Medical Oncology- KFSH&RC- Riyadh*

OBJECTIVES:

- Establish the maximal tolerated dose and the dose limiting toxicity (DLT) of the combination of bi-weekly Irinitecan, Capecitabine, and Cetuximab in the 1st line treatment of advanced colorectal cancer.
- Evaluate the response rate and toxicity profile of the above combination.
- To assess Progression Free Survival (PFS), Overall Survival (OS) of the above combination.

CURRENT STATUS: Patient Recruitment phase.

CYSTIC FIBROSIS PROJECT

PROJECT TITLE: Cystic Fibrosis Registry
RAC# 2111016

PRINCIPAL INVESTIGATOR: *Dr. Hanaa Banjar. MD, FRCPC, Consultant Paediatric Pulmonology - KFSH&RC- Riyadh*

OBJECTIVES:

- To obtain the incidence, prevalence and patterns of CF diseases in KFSH&RC and later in the Kingdom of Saudi Arabia.
- To identify the risk factors associated with CF diseases
- To document the treatment procedures and assessment of treatment outcome.

ORA APPROVED PROJECTS

- Dr. AbdulKarim AlHakeem, Assistant-Consultant, Pediatric Gastroenterology- Vitamin D deficiency in CF patients at KFSH&RC: (RAC# 2151171), Presented in the 2nd Cystic Fibrosis conference 3–5 November 2015, KFSRC, Riyadh, and also presented in the 5th Annual Middle East Congress on clinical Nutrition, 22–24 March 2016, Cairo, Egypt.
- Dr. Najlaa AbdulAziz - liver disease in CF patients at KFSH&RC: (RAC# 2151155), Presented in the 2nd Cystic Fibrosis conference 3–5 November 2015, KFSH&RC, Riyadh, and also presented in the 9th KFSH&RC Residents Research day, 18 February 2016.

- Ms. Dhefaf Al-Abdaly, Research Coordinator- Demographic data of CF patients at KFSH&RC: (RAC# 2151150), Presented in the 2nd Cystic Fibrosis conference 3–5 November 2015, KFSH&RC, Riyadh.
- Dr. Maryam Dabbour, R2-Vitamin A, E, K in CF patients at KFSH&RC: (RAC# 2151170), Presented in the 2nd Cystic Fibrosis conference 3–5 November 2015, KFSH&RC, Riyadh, and also presented in the 9th KFSH&RC Residents Research day, 18 February 2016.
- Dr Sharifa AlZafiri, fellow- Pediatric Gastroenterology - Nutritional Data of CF patients at KFSH&RC: (RAC# 2151176), Presented in the 2nd Cystic Fibrosis conference 3–5 November 2015, KFSH&RC, Riyadh, and also presented in the 9th KFSH&RC Residents Research day, 18 February 2016.
- Dr Sara AlBanyan- R1-Cystic Fibrosis related Diabetes, KFSH&RC: (RAC# 2111 016), presented in the 9th KFSH&RC Residents Research day, 18 February 2016.

CURRENT STATUS: Ongoing retrospective study with 394 registered patients

PRIMARY IMMUNODEFICIENCY DISORDERS – QUALITY OF LIFE

PROJECT TITLE: Subcutaneous Immunoglobulin (SCIg) Replacement Therapy

PRINCIPAL INVESTIGATOR: *Bandar K Al Saud MBBS,FRCPC - Allergist/ Immunologist Department of Pediatric - KFSH&RC- Riyadh*

Subcutaneous immunoglobulin (SCIg) replacement therapy is an alternative for patient on intravenous immunoglobulin replacement. It gives the patient the freedom from coming to the hospital every 3–4 weeks for a 4 to 6 hours infusion. At our hospital we are working on adding SCIG to our hospital formulary and I am leading the working group task force. One of the idea is to conduct prospective controlled open label study looking at the safety, efficacy, and cost effectiveness in our patients population. We can also look at to assess health-related quality of life.

CURRENT STATUS: In the process of buying the research questionnaires (SF-36v2 Health Survey and CHQ-PF50).

DISEASOME RESEARCH GROUP

HEAD

Dilek Colak, PhD

MEMBERS

Olfat AlHarazi *(Grant Employee)*

Parvez Siddique *(part-time)*

Sukina Qanbar *(part-time)*

Muzaffar Hussain *(part-time)*

THE MISSION OF THE DISEASOME RESEARCH GROUP (DRG) IS TO focus on research, services and teaching and training in the areas of computational genomics and disease genomics and to provide computational and statistical support to clinical, applied, translational, and biomedical researchers for identifying better and more accurate markers for disease diagnosis, prediction of prognosis and therapeutic outcome in Saudi population. Our research projects are related to development and application of statistical and computational genomics techniques to better understand human diseases and the mechanisms underlying them, including several complex diseases, such as cancer, autism, unknown chromosomal disorders, cardiovascular disease, metabolic and developmental diseases and others. Genome-wide molecular measurements, data mining, and bioinformatics approaches have provided the means to explore human diseases from a molecular basis. The integrated analysis of genome-wide molecular measurements with the molecular networks of interaction is a powerful approach for understanding molecular architecture of diseases.

SELECTED ACHIEVEMENTS

1. In year 2015, we have published over 16 publications (original research articles, review articles and abstracts).
2. Received the first prize award at the Third International Genomic Medicine Conference, Jeddah, KSA, Nov. 2015 in a poster competition among 200 posters (participants from USA, UK, Spain, Germany, and others). The jury consisted of world renown scientists: Prof. Jerry Shay (University of Texas Southwestern Medical Center Dallas, USA), Prof. Albert Fornace (University Washington DC, USA), Stephen Scherer (The Hospital for Sick Children and University of Toronto, Ontario, Canada), Sudhir Kumar (The Biodesign Institute Arizona State University, Tempe, Arizona, USA) and Prof. Anna Goodeve (Department of Cardiovascular Science University of Sheffield, Medical School, UK).
3. Four original research articles will be nominated for the "Best Publication Award for 2015" at KFSH&RC Annual Research Report day.
4. Participated/collaborated in over 10 RAC-approved/KACST funded projects.
5. Dr. Colak has served in the Editorial board of two peer-reviewed international journals, namely Genomics and PloS One, and has been invited to participating in the organizing committee of an international conference on genomic medicine, which will be held in USA.

SELECTED RESEARCH PROJECTS

PROJECT TITLE: The Saudi-Arab Diseasome - A Network of Diseases: A Comprehensive Integrated Network-based Analysis Using Genomic, Transcriptomic and Proteomic Data Sets for Identification of Potential Markers for Diagnosis, Prognosis, and Therapeutic Outcome for Saudi Diseases

RAC# 2110 006

FUNDING: National Plan for Science, Technology and Innovation program (NSTIP/KACST)
PROJECT CODE: 11-BIO2072-20

INVESTIGATORS: *D Colak (PI), N Kaya, AA Alaiya, M Dagestani, SM Amer, B Karakas, and N Dzimiri, A AlQahtani*

PROJECT DESCRIPTION: In this project, we identify subnetwork markers for diseases in the Saudi/Arab population using integrated network-based approaches. We use biomolecular data sets (genome-wide gene expression profiles, Single Nucleotide Polymoprhisms (SNPs) and Copy Number Variations (CNVs), proteomics based protein profiles) that the collaborators of this project previously studied in other approved projects as well as other publicly available datasets at the genomic databases for diseases such as several types cancers (breast cancer, liver cancer), neurological disorders, metabolic disorders, cardiovascular diseases and others. Our results will elucidate the relationships among those diseases at the molecular level. We will create the first Saudi/Arab "Diseasome", a network of diseases; hence to identify how closely all disease disorders similar/distinct from each other and elucidate common molecular origin of several disorders. The projectis led by Dilek Colak, Ph.D. (BESC) in collaboration with investigators from Molecular Oncology, Genetics, Stem Cell Therapy Program, Infection and Immunity, as well as with international collaborators from Dana Farber Cancer Institute, Harvard School of Public Health, and Wayne State University.

PROJECT TITLE: Molecular Studies on Hereditary Ataxias in Saudi Arabia: A Multicenter Study Utilizing Exome Sequencing Coupled with Homozygosity Mapping for Clinical and Diagnostic Use

KACST#14-MED2007-20
FUNDING: National Plan for Science, Technology and Innovation program (NSTIP/KACST)

PROJECT CODE: 14-MED2007-20

INVESTIGATORS: *N Kaya, A Alhashem, D Colak, E Faqeih, M Alfadhel, M Al-Muhaizea, M Salih, H Aldhalaan*

PROJECT DESCRIPTION: Ataxias are group of disorders characterized by slowly progressive incoordination of gait and often associated with poor coordination of hands, speech, and eye movements. In this project, we will identify families inflicted with autosomal recessive ataxias (ARA) based on the symptoms, clinical and familial history and family pedigree. Then main objectives are to identify genes and mutations causing the ARA using latest technologies, such as exome sequencing coupled with autozygome mapping. Then we will develop a comprehensive gene panel for ARAs using targeted next-generation sequencing technologies. The project is recently approved for funding by KACST/NSTIP.

PROJECT TITLE: Molecular Studies on Mitochondrial Diseases in Saudi Arabia
FUNDING: National Plan for Science, Technology and Innovation program (NSTIP/KACST)
PROJECT CODE: 11-BIO2221-20

INVESTIGATORS: *N Kaya, M Al-Owainm M. Al-Muaizea, H. Al-Hindi, H. Al-Zaidan, M. Al-Dosari, M. Alfadhel, D. Colak*

PROJECT DESCRIPTION: Establishing a diagnosis in patients with a suspected mitochondrial disorder is often a challenge because of the extreme clinical and genetic heterogeneity of these conditions. The true prevalence of mitochondrial disorders is difficult to ascertain in the Kingdom of Saudi Arabia (KSA) since this entity is undoubtedly underreported, but it is expected to be higher than in other populations due to high consanguinity, and the tribal nature of the society. This project represents the first comprehensive mitochondrial research project in KSA. Our main aim is to ascertain patients with suspected mitochondrial disorders with subsequent identification of the disease causing mtDNA or nuclear gene/mutations using state of art molecular approach and technologies. We expect to characterize novel nuclear genes causing mitochondriopathies that will shed light for other researchers on molecular mechanisms of such diseases and could ultimately lay the ground for potential therapies in the future. In addition, our results will have significant impact on drawing the mutational landscape of mitochondrial disorders in KSA. Furthermore, the knowledge gained from our study will be utilized by molecular laboratories in KSA for diagnosis of these conditions. Finally, the results will be the basis for a preventative program for mitochondrial genetic diseases.

PROJECT TITLE: Genomics, Transcriptomics, and Proteomics Analysis of Ovarian Hyperstimulation Syndrome: A comprehensive Molecular Look to a Complex Syndrome
RAC# 2100 002
FUNDING: KSU-KACST Joint Grants Support for Center of Excellence

INVESTIGATORS: *M Dagestani, N Kaya, D Colak, S Coskun, NA AlEissa, MH Daghestani, KA Awartani*

PROJECT DESCRIPTION: Ovarian hyper stimulation syndrome (OHSS) usually is an iatrogenic exaggerated response and could be a potentially life-threatening during ovarian stimulation treatments. With our full scale genomics study to understand this complex syndrome, we expect to find important and critical findings that will help better understanding of the disease in addition to potential findings for prevention of OHSS. Also we expect to find some genes or markers linked to the disease causing/susceptibility regions and factors that can be further evaluated as likely biomarkers for the treatment of this disease.

PROJECT TITLE: Identification of the Mutational Spectrum and Frequencies of BRCA1 and BRCA2 Genes in Saudi Breast and Ovarian Cancer Populations
FUNDING: KACST/NSTIP (12-BIO2947-20)

INVESTIGATORS: *B Karakas, A Aboussekhra, D Colak, T Al-Tweigeri, A Tulbah*

PROJECT DESCRIPTION: BRCA1 and BRCA2 (BRCA1/2) genes are heavily involved in mammalian cell DNA repair process. Therefore, the loss of function in either protein causes genetic instability and subsequent cancer development in breast (BC) and ovaries (OC). To identify the frequency of these genes mutations in the region, we will sequence all the coding exons of both BRCA1/2 genes Arab BC and OC patients by next generation sequencing and verify by Sanger sequencing.

PROJECT TITLE: A Non-invasive and Sensitive "Molecular Blood Assay" to Evaluate Treatment Response/ Relapse in Women with Breast Cancer
FUNDING: KACST

INVESTIGATORS: *B Karakas, A Aboussekhra, D Colak, T Al-Tweigeri, A Tulbah, O Demirkaya, A Abukhadeir*

PROJECT DESCRIPTION: Early diagnosis, measurement of response to therapies and relapses following therapies are evaluated mostly through imaging techniques (e.g., mammography and magnetic resonance imaging (MRI), etc). However, these techniques are expensive and usually expose the patient to radiation, which raises concerns regarding patient safety. In this project, we propose to test a recent emulsion PCR technique for the detection of rare blood circulating mutant DNA as a biomarker for breast cancer therapy and relapse. We will initially determine the mutation profile within a woman's breast cancer (tissue biopsy) and then use these predetermined mutations to monitor treatment response and possible relapses.

PROJECT TITLE: Molecular Genetic Studies in Chromosome Disorders
RAC# 2040 042

INVESTIGATORS: *Kaya N, Colak D, Sakati N, Al-Odaib A, Fowzan Alkuraya, Al-Dosari N, Walter C, Hasnen Z*

PROJECT DESCRIPTION: The specific aim of this project is to identify an abnormality in chromosomes of patients with dysmorphic syndromes clinically suspected to have a chromosome disorder or possibly inherited in families with more than one affected dysmorphic syndrome.

PROJECT TITLE: Proteomic Analysis of Human Breast Cancer Stem Cells/Progenitor Cells
RAC# 2080021

INVESTIGATORS: *Alaiya A, Tulbah A, Adra C, Colak D, Al Dayel F, Ghebeh H, Al Humaidan H, Zimmarmann JG, Al Mansouri L*

PROJECT DESCRIPTION: In mouse models, it has been proven that breast cancer stem cells exclusively retain the ability to form new tumors and they display stem/progenitor cell properties. They have been recently isolated and propagated *in vitro*, and recognized as CD44+CD24- breast tumor cells. The goal of this study is to investigate the critical molecular alterations affecting breast cancer stem cells, and how they interact with their microenvironment and the phenotypic characteristics of mammary stem cells will be defined at the protein level, using proteomics approach.

PROJECT TITLE: Positional Cloning of Genes Underlying Genetics Disorders with Prominent Neuro-Developmental Manifestations in Several Extended Families
RAC# 2060 035

INVESTIGATORS: *N Kaya, D Colak, and M Al-Sayeed*

PROJECT DESCRIPTION: The specific aim of this project is to determine gene(s) ore regions that are critical and likely to play a role on the manifestations of genetic disorders with prominent neurodevelopmental features. We will utilize high density Affymetrix 500K SNP chips to perform genotyping, copy number analysis, linkage, homozygosity mapping, targeted sequencing on the patients' samples.

PROJECT TITLE: Role of RORγt Transcription Factor in the Immune System Development, Autoimmunity and Transformation
RAC# 2080 046

INVESTIGATORS: *Abbas Hawwari, G. Matic, N Kaya, D Colak, N Al-Dosari*

PROJECT DESCRIPTION: RORγt, a member of the hormone nuclear receptor super family, is a transcription factor that activates or suppresses many genes. The function of RORγt was studied in multiple mouse models that are deficient in RORγt. RORγt-/- mice lacks both RORγ and RORγt (an isoform variant of RORγ) and RORγtGFP/GFP mice that do not express RORγt but express EGFP instead. These mouse models showed that RORγt expression is restricted exclusively to a limited number of cell types in the immune system, specifically: double positive (DP) thymocytes, lymphoid tissue inducer (LTi), crypto patches (CP), isolated lymphoid follicles (ILF), and T helper -17 (Th17) cells. RORγt was shown to be indispensible for the development of secondary immune organs such as Peyers patches (Pp), and lymph nodes (LN). Other defects due to RORγt loss are also observed: proliferation/apoptotic defects in DP thymocytes, inefficient DP thymocytes development, lack of CP and ILF, enlarged spleen and absence of Th17 cells. Moreover, RORγt is implicated in the development of autoimmune diseases and thymic lymphoma. Our knowledge of the molecular mechanisms by which RORγt controls the development of immune cells, organs and structures and protect against autoimmunity and thymic lymphoma is lacking. This proposal is a step towards a better understanding of these mechanisms. We think that in order to understand these processes, we need to understand: first, what controls RORγt expression and why it is restricted to only small numbers of immune cell types; second, the genes that are regulated by RORγt; and third, what proteins interact with RORγt to facilitate its function. This understanding will help us understand, not only the development of DP thymocytes, LN, Pp, CP, ILF, and Th17, but also the process by which RORγt protects us against autoimmune and lymphoma diseases. On the long run, this information will help in the diagnosis, drug design and treatment of such diseases in human in a similar fashion to the success story with estrogen receptor and breast cancer.

PROJECT TITLE: micro RNAs as Biomarkers for Diagnosing Breast Cancers
RAC# 2110016

INVESTIGATORS: *Suad M bin Amer (PI), Ahmad Yaqinuddin, MD, Colak D, Osama Ahmed Al Malik, Taher AL-Tweigery, Asma Tulbah*

PROJECT DESCRIPTION: Breast Cancer remains one of the commonest cancers affecting women worldwide. To date several genetic, epigenetic (e.g. DNA methylation), as well as proteinaceous biomarkers have been found to be associated with the disease but their utility as robust indicators of disease remains uncertain. In light of this, there is a need to identify robust, specific as well as sensitive biomarkers that will be useful for detecting breast cancers and differentiate between aggressive vs non-aggressive tumors. Micro-RNAs (miRs) are small 18-24 nucleotide RNAs which regulate

the expression of approximately 30% of human genes and whose expression is frequently dysregulated in cancers. Contributions from a number of laboratories have demonstrated that different cancers are associated with distinct miR profiles. Given that miRs are stable in serum, our goal is to identify a discrete set of miRs that are breast cancer-specific and which can therefore be employed as disease predicting biomarkers.

PUBLICATIONS

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- Ranad Shaheen, Shams Anazi, Tawfeg Ben-Omran, Mohammed Zain Seidahmed, L. Brianna Caddle, Kristina Palmer, Rehab Ali, Tarfa Alshidi, Samya Hagos, Leslie Goodwin, Mais Hashem, Rehab Ali, Salma M Wakil, Mohamed Abouelhoda, Dilek Colak, Stephen A. Murray, Fowzan S Alkuraya, "Mutations in SMG9, encoding an essential component of the nonsense-mediated decay machinery, cause a multiple congenital anomaly syndrome in human and mouse", *American J of Hum Genetics*, 2016 Jan. (in press).
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- Al-Hassnan ZN, Al-Dosary M, Alfadhel M, Faqeih EA, Alsagob M, Kenana R, Almass R, Al-Harazi OS, Al-Hindi H, Malibari OI, Almutari FB, Tulbah S, Alhadeq F, Al-Sheddi T, Alamro R, AlAsmari A, Almuntashri M, Alshaalan H, Al-Mohanna FA, Colak D, Kaya N., "ISCA2 mutation causes infantile neurodegenerative mitochondrial disorder". *J Med Genet*. 2015 Mar;52(3):186-94. doi: 10.1136/jmedgenet-2014-102592. Epub 2014 Dec 24.
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SCIENTIFIC COMPUTING SECTION

HEAD

Anas Al-Halees, PhD

MEMBERS

Mansoor Ali Baig
Fahad Al-Enazi
May Al-Husseini
Muzaffar Hussain
Yousef M. Hussain
Shoukath Raza
Arnie Tayco

SCIENTIFIC COMPUTING UNIT IS A CORE FACILITY WITHIN THE Department of Biostatistics Epidemiology and Scientific Computing (BESC). The mission of the Scientific Computing section is to develop and maintain in-house databases of a technical/research nature, which can be used for research purposes or clinical research registries. The facility provides instruction on the use of developed databases and is committed to design and develop scientific software applications, databases and registries on request.

The section also provide user trainings, end user IT/Desktop support, IT related adhoc requests and and software implementations within the Research Centre environment.

APPLICATIONS (DEVELOPED/BEING DEVELOPED YEAR 2015)

I2B2 PLATFORM EVALUATION AND CONFIGURATION

Scientific Computing unit had taken an initiative which would translate into a hospital wide translational research platform. The task was to study and evaluate the I2B2 (Informatics for Integrating Biology & the Bedside) which is an open source platform.

It is a scalable informatics framework that will enable clinical researchers to use existing clinical data for discovery research and, when combined with IRB-approved genomic data, facilitate the design of targeted therapies for individual patients with diseases having genetic origins.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

INSTALLING AND CONFIGURING REDCAP PLATFORM

Scientific Computing has successfully implemented the RedCap Rapid application development platform which can be used hospital wide for basic databases and surveys.

PROJECT IN-CHARGE: *Dr. Anas Al-Halees*

INSTALLATION AND IMPLEMENTATION OF MENAITECH HRMS

Scientific computing was deeply involved in imaplementing the MenalTech HRMS solution for the grant staff within the hospital. There was a need to maintain the HRM data within the research center for the grant staff, as the related data is not captured under the Oracle HRMS used by the hospital.

PROJECT IN-CHARGE: *Dr. Anas Al-Halees*

IMPLEMENTING A WEB APPLICATION FOR IARED

PROJECT IN-CHARGE: *Dr. Anas Al-Halees*

PEDIATRICS CLINICAL INFORMATION SYSTEM

Scientific Computing has successfully developed and implemented the Pediatrics clinical information system which for the department of Pediatrics, to capture the daily minimum essential data set components including the demographics data, primary and secondary diagnosis and follow-up status.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

SECURING THE RC WEBSERVER AND ITS APPLICATION

There was a need to secure the application used by the research center, scientific computing has indentified and secured all the necessary application which has be accessed through the internet.

PROJECT IN-CHARGE: *Dr. Anans Al-Halees, Mansoor Ali Baig, Fahad Al-Enazy*

CYSTIC FIBROSIS REGISTRY

Scientific Computing unit was actively involved in designing the cystic fibrosis registry using the REDCAP rapid application development platform.

PROJECT IN-CHARGE: *Mansoor Ali Baig, Dr. Anans Al Halees*

SUPPORT FOR INTRONIC AU-RICH ANALYSIS

PROJECT IN-CHARGE: *Dr. Anas Al-Halees*

UNITED NATIONS DEVELOPMENT (UNDP) PROJECT – SAU10-82003: SUPPORT TO THE SAUDI FDA

BESC/Scientific Computing section member participated as a senior technical consultant for the committee formed with an objective to write the specifications, policies and requirements of the National Reister of medical devices planted in the human body for United Nations Development Programme (UNDP) Project SAU10-82003.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

APPLICATIONS RE-DEVELOPED / UPGRADED / MODIFIED

SCIENTIFIC COMPUTING UNIT (SCU) staff is well aware of the current technology trends available in the market and strive to keep themselves updated to the latest technological update. With the advent of the STABLE versions of Microsoft .NET (VS 2008 VS 2010), SCU has been upgrading most of its projects on an ongoing basis to get the best out of the technology and infrastructure available. Most of the projects developed before 2005–2006 we developed using Microsoft ASP technology with SQL Server as the backend.

SCU has planned to provide a technology upgrade to the older projects and convert and port this application on a ASP.NET or Enhance the applications to include more dynamic capabilities using AJAX. This upgrade will improve the application security, reliability, performance.

PERFORMANCE EVALUATION SYSTEM

SCU was partially involved in the developing and upgrading the performance management system(Grade 12 and above) for the research center, this system provides the measure/rating of the annual staff performance within the set Key Performance Indicator(KPI) framework designing by the research center, and also documents the achievements which would match with the performance planning done by the employee.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

CONGENITAL HEART DEFECTS REGISTRY

The CHD Registry was developed based on .Net Framework version 2.0, using Visual Studio 2003, the registry was upgraded using Visual Studio 2010 on to .net Framework 3.5, the VS 2003 architecture being completely different, it was a challenging task to upgrade the application, which needed to clear more than 800 compatibility issues.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

UPDATE IN PRIMARY IMMUNO DEFICIENCY REGISTRY.

Certain Coding was performed on some standard variables in various forms throughout the registry and the current data was updated in accordance to the new codes.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

MINOR UPDATES/UPGRADES FOR THE BIO-TECHNOLOGY PROJECT MANAGEMENT SYSTEM FOR THE BIOTECH SCIENCE & TECHNOLOGY UNIT

This is a project built for the research Center administration / Finance for handling all the biotech projects with KACST. It is a project management tool for the principle investigators, co-investigators, RC finance and admin to manage their project from a financial perspective. This Idea is intended to be upgraded soon to make this system go nationwide for all research projects. The upgrades included special reports, graphs and some upgrades on various levels.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

ONGOING PROJECTS (USER SUPPORT & MAINTENANCE)

MAINTENANCE OF TRC PLATFORM

BESC is heading the project to include translational research capabilities winthin the Research Centre, on of the products chosen is the Oracle Health Sciences Translational Research, which is also an initiative towards personalized medicine. The comprehensive platform enables secondary use of electronic health records/Genomic data and other data sources to help accelerate biomarker identification for drug discovery, clinical development and translational medicine.

PROJECT IN-CHARGE: *Anas Halees, Shoukath Raza*

HELP DESK AND TECHNICAL SUPPORT

BESC/Scientific Computing is involved in providing helpdesk and technical support to the Research Centre facilities which also includes the end user support. Technical support covers PC maintenance, software installations, configuration and other trouble-shooting issues. SC acts as first level support by facilitating instant solutions avoiding delays caused in approaching HITA technical support.

PROJECT IN-CHARGE: *Arnie Tayco, Yousef Hussain, Muzaffar Hussain*

ARABIAN HORSES WEB APPLICATION

Saudi Diagnostic Laboratory (SDL), which is located in KFNCCC&R, receives and processes samples of horses for DNA-fingerprinting and parentage-testing. These samples are received from King Abdulaziz Arabian Horses Centre (KAAHC). An application is being developed to manage data of horses, their samples, requested tests and reports. Rich-Format reports will be generated using this browser-based application that will be available to SDL and KAAHC though Internet. Application provides features to upload unlimited pictures of horses those are registered with this application. An internal messaging system was also developed and incorporated on client's request to maintain log of communication between both the stakeholders.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

BILLING DATA MANAGEMENT SYSTEM

Research Centre provides its clients services, products and laboratory test facilities. Clients are charged according to their contract (between client and RC). Billing Data Management application was developed with the urge:

- To keep track of all rendered services, supplied products and laboratory test performed.
- To keep track of all bills to the clients and receipts against those bills.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

THROMBOEMBOLIC REGISTRY (TEDR)

Thromboembolic Disorder Registry is a web-based application. It was re-developed for TED users. This database allows for stratification to look at complications in subgroups of patients which may lead to an overall improvement in patient care and health care planning. The functions provided in this application are: Managing patient, Searching for patient with a given criteria, Generating patients report, Generating charts and data Exporting. It allows the user with the administrative level to managing the user of the system.

PROJECT IN-CHARGE: Mansoor Ali Baig

NEURAL TUBE DEFECTS REGISTRY (NTDR)

The Neural Tube Defects Registry is a national registry that serves as a source of data on NTD. The currently running application is developed by the SCU using ASP Technology.

In order to provide users with high performance applications and keep up to date with the latest technologies, the NTDR is redeveloped using ASP.Net. The functions of the newly developed NTDR include adding/editing/deleting patients' forms, searching for specific data, exporting data and generating charts. In addition to the enhanced security features that manage the use of the system and maintain the confidentiality of patients' information.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

EPILEPSY REGISTRY

The Epilepsy Registry is a national registry that manages Epilepsy patients' data. The currently running application is developed by the SCU using ASP Technology. In order to provide users with high performance applications and keep up to date with the latest technologies, the Epilepsy was redeveloped using ASP.Net. The functions of the newly developed Epilepsy include adding/editing/deleting patients' forms, searching for

specific data, exporting data and generating charts, and reports.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

THERMO LUMINISCENT DOSIMETRY (TLD)

Thermo Luminiscent Dosimetry (TLD) Database Application Bio-medical Physics Department issues and monitors TLD items to its clients for radiation safety. The existing old database is unable to fulfill the increasing requirements. A new database application developed to keep track of:

- TLD items (Badges/Rings) issued to participants.
- Items received from participants.
- Keep readings and calculated dose after evaluation of TLD items.
- Generation of different reports and barcode labels.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

NATIONAL LABORATORY FOR NEWBORN SCREENING

We have developed & designed a database, which comprises of Web-based forms & reports connected to an SQL database running on a dedicated central server with extensive security and database features. This application provides features to register the patients while entering their sample's information to the database. Reports results are entered and rich-formatted reports can be generated using Internet browser.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

SAUDI THROMBOSIS AND FAMILIAL THROMBOPHELIA REGISTRY

The web implementation for Saudi Thrombosis and Familial Thrombophelia Registry (S-TAFTR) is designed by SCU. The application is designed to be used nation-wide, providing real-time reports, charts, and data export facilities.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

THROMBOEMBOLIC DISORDERS REGISTRY

This is a hospital-based registry with national registry features. We are collaborating with Registries Core Facility in maintaining and designing this Web based clinical registry.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

CYCLOTRON MAINTENANCE DATABASE

Development and successful implementation of web-based application to keep track of the maintenance related record of all the production and testing equipment being used in Cyclotron and Radiopharmaceuticals Department. The application also generates schedules of maintenance and calibrations.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

NEUROMUSCULAR DISEASES REGISTRY

The web implementation for Neuromuscular Diseases Registry (NMDR) is designed by SCU in 2004. The application is designed to be used nation-wide, providing real-time reports, charts, and data export facilities and currently under second phase of testing.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

RARE DENTAL DISORDERS REGISTRY

The Rare Dental Disorders Registry (RDD) of the King Faisal Specialist Hospital and Research Centre (KFSH&RC) was established in 2010 as a collaborative effort between the Department of Biostatistics, Epidemiology and Scientific Computing and the Department of Dentistry.

The registry aims in collecting patients with the following disorders:

- Ectodermal Dysplasia
- Papillon-Lafevre syndrome
- Amelogenesis imperfecta
- Dentinogenesis imperfect
- Cleidocranial dysplasia
- Hypodontia/aplasia

PROJECT IN-CHARGE: *Mansoor Ali Baig*

RESEARCH CENTRE CREDENTIALS COMMITTEE

Research Centre Credentials Committee database is provides an online web application for authorized RCCC members to make comments and recommendations for applicants. The application is also provides online view for the applicants credentials documents to view and make the decision.

PROJECT IN-CHARGE: *Fahad Al-Enazi*

RENAL TRANSPLANT DATABASE

Web based application enable authorized user to add edit information for patients. The information include (Demographic, Transplant, History, Donor, Biopsy, Complication, and Follow up) data. The application provide export feature to the user to make their own statistics using SPSS software.

PROJECT IN-CHARGE: *Fahad Al-Enazi*

OLIGONUCLEOTIDE SYNTHESIS ORDERING

King Faisal Specialist Hospital and Research Centre provides processed primers to researcher working in the hospital or out of the hospital. This core facility receives requests from and prepares primers for several KFSH&RC Researchers and Non-KFSH&RC Researcher on daily basis. All requesters are required to get registered themselves before order placement. The application retrieves the orders from the database after every few minutes. So the orders are presented to the laboratory staff for processing selection automatically after their submission.

PROJECT IN-CHARGE: *Fahad Al-Enazi*

RE-ENGINEERING THE NATIONAL FAMILY SAFETY REGISTRY APPLICATION.

This application provides Electronic Forms designed and implemented in order to accept data related to patients with abuse history. This data is entered electronically and later on, the users will have the privileges to view it at any time and on different machines. In addition to viewing those data, the users are allowed to do some modifications when necessary.

PROJECT IN-CHARGE: *Mansoor Ali Baig*

USER'S TRAINING

SCU builds database applications (Mostly web based) that serve as effective tools for data retrieval, analysis, planning, and decision support. Our database development is Web-centered for Internet and intranet deployment.

SCU is dedicated to impart a comprehensive training tailored according to the program for the candidates to understand the software development concepts along with real time implementation of a software development project.

SOFTWARE TOOLS USED

- Backend Databases: MS SQL Server 2000–2008/ MS Access
- Scripting Languages: ASP Classic, VBScript, HTML, XML, JavaScript
- Programming Platform: Microsoft Windows IIS with .NET Framework 2.0-4.0, MVC
- Programming Languages: ASP.NET (with VB.NET), Visual Basic, Ajax
- Development Tools: Visual Studio.NET 2005–2010, Visual Studio 6.0, Adobe Photoshop
- Training Plan Scope
- Evaluation & direction
- Covering the concepts of Software Engineering
- Concepts of Database Design and development
- Discussing the software development lifecycle with the software project Management perspective
- Learning UI design and scripting
- Design & develop web based applications
- Project System Requirements Documentation
- Project Presentation

BIOMEDICAL PHYSICS DEPARTMENT

BIOMEDICAL PHYSICS DEPARTMENT

CHAIRMAN

Belal Moftah, PhD, FCCPM

DEPUTY CHAIRMAN

Refaat Al-Mazrou, MSc, FIPEM

STAFF MEMBERS

AlAnazi, Ibrahim, MSc, ABHP, ABMP
AlAssailan, Dena
AlBuhairi, Muneera, BSc
AlDelaijan, Saad, MSc
AlEdan, Noor, BSc *(RC Grant)*
AlGain, Ibrahim, MSc
AlGhamdi, Huda, BSc *(RC Grant)*
AlHadyan, Khaled, MSc *(on study leave)*
AlHarbi, Najla, BSc
AlHumidan, Heba, BSc
AlJamaan, Saad, BSc
AlKafi, Mohd Abdullah, MSc, DABR
AlMohammed, Huda, CMD, PhD – *Resignation: 25 July 2015*
AlMoussa, Akram, MSc *(Head)*
AlMusallam, Jameelah, BSc *(RC Grant)* – Resignation: 12 August 2015
AlMutairi, Najla, BSc *(Trainee)*
AlNajjar, Waleed, PhD, DABR, ABMP *(Head)*
AlQahtani, Khaled, BSc *(SCDP Trainee)*
AlSbeih, Ghazi, MD, PhD *(Section Head)*
AlSelham, Hind, MSc
AlShora, Shaima, BSc *(RC Grant)*
Altwaimi, Maiz, BSc *(Tainee: until 1 August 2015)*
AlWatban, Adnan, PhD, FIPEM
AlZorkany, Faisal, MSc
Arib, Mehenna, PhD *(Head)*
Ashmeg, Sarah, BSc *(on study leave)*
Awidh, Manal, BSc, CMD *(RC Grant)* – Resignation: 11 April 2015
Bin Judia, Sara Saif, BSc
Castro, Jenelyn, BSc *(RC Grant)*
Demirkaya, Omer, PhD, DABNM *(Section Head)*
El-Ewisy, Sara Mahmoud, BSc *(RC Grant)*
Hassad, Osama, BSc, CMD
Hassan, Zeinab, PhD – *Resignation: 05 October 2015*
Helmi, Arwa, BSc
Higby, Christine, MA, CMD – *Resignation: 21 January 2015*
Hussain, Muhammad Abrar, PhD, DABR
Lagarde, Celestino, BSc
Mahyoub, Fareed, MSc, MIPEM *(Section Head)*
Mishra, Krishnanand, PhD *(RC Grant – Int'l)*
Mohammad, Mohammad Awad *(RC Grant)*
Mohtasib, Rafat, PhD *(Section Head)*
Mosallay, Huda Abdelrahman, BSc *(RC Grant)*
Mwidu, Umar, MSc, DABR
Nazer, Ghadeer, BSc, CMD
Nobah, Ahmad, MSc, DABR
Noor, Omar, MASc
Reyes, Eddie delos
Safar, Wedyan Mohammed, BSc, CMD
Santos, Rikka Maureen, MSc
Shehadeh, Mamoun, MSc, DABR
Shetaya, Hanan, BSc *(RC Grant)*
Venturina, Nikki, BSc *(RC Grant)* – *Resignation: 30 Sept. 2015*
Veridiano, Josephine, BSc
Wadi-Ramahi, Shada, PhD, DABR

The activities of the Biomedical Physics Department for the year 2015 are largely associated with the services we provide for clinical departments in support of quality patient care. Moreover, we have been actively involved in clinical and basic research, continuing education and various income producing activities in the different areas of Biomedical Physics. The Department has continued to play a major role for the success of radiotherapy patient treatments and diagnostic imaging procedures through the introduction and implementation of state-of-the-art techniques, and maintaining a radiation-safe environment for all KFSH&RC personnel, patients and the general public through our radiation safety programs. We promote a broad range of connections and partnerships with recognized clinical and research departments and organizations. Our collaboration with these groups helps us secure our position as one of the leading institutions nationally and internationally in the field of health care.

The summary of key and major achievements of the Biomedical Physics Department during this reporting period includes the following:

- Major role in the effective and safe clinical utilization of the six major radiotherapy treatment modalities namely, TomoTherapy, CyberKnife, TrueBeam, Mobetron, Nucletron HDR and IntraBeam Intraoperative Radiotherapy system for cancer patients.
- Primary organizer of the 2015 Radiation in Medicine Symposium and Workshops, from 24-26 February 2015.
- Completion of the 5-week Medical Physics and Radiation Protection Training Course for the Ministry of Health staff. Four groups were trained, each group had 25 trainees and they started from December 2014 until May 2015.
- Ongoing activities for the first "IAEA/ARASIA Regional Residency Training Program for Medical Physicists in Radiation Oncology at KFSH&RC". Training completion of 3 residents.
- Co-Authoring the prestigious IAEA Postgraduate Medical Physics Academic Programs endorsed by the International Organization for Medical Physics.
- Leading of efforts for re-accreditation of our radiation physics procedures, machine output and the American RTOG protocols by the Imaging and Radiation Oncology Core (IROC) of M.D. Anderson Cancer Center.
- Ongoing activities for the first KFSH&RC and IAEA Collaborating Centre in the Kingdom and in the region. This includes conducting of a joint KFSH&RC and IAEA Workshop entitled QUATRO and QUADRILL workshops.
- Residency program in Nuclear Medicine Physics which is supported by the IAEA and the King Abdullah City for Atomic and Renewable Energy (KACARE) this year and is under review.
- Participated in the IAEA code of practice of small beam dosimetry that will start soon.
- Completion of final report for KACST project entitled "Developing biological dosimeters for the assessment of radiation overexposure in nuclear accidents".
- Our KACST Biotechnology grant was scored highly (13/15) by the American Association for the Advancement of Science (AAAS) in USA, the publisher of the premier global Science weekly, and was designated a 'model' grant proposal for other researchers by the Director of KFSH&RC Biotechnology Unit.
- Approval and recipient of fund from KACST for our project titled: Advanced magnetic resonance imaging (MRI) for patients with mild cognitive impairment (MCI) and patients with Alzheimer's disease (AD).
- Ongoing in-house training, normally done through a lengthy training programs abroad, that made a number of the Department staff board certified by internationally recognized board

certifying bodies such as the American Board of Radiology (ABR), and Medical Dosimetry Certification Board (MDCB). One member of our Radiation Oncology Physics team passed the prestigious ABR board certification exam during this reporting period.

- Key role in several other major projects, including the mega Proton-Carbon Ion Therapy (PCIT) project as well as the radiological (radiology and radiotherapy) equipment procurement and shielding designs for King Abdullah Center for Oncology and Liver Diseases (KACO&LD).
- Major upgrade of the Secondary Standard Dosimetry Laboratory (SSDL) which will allow our SSDL facility to continue to play a major role in providing secondary standard calibration across the Kingdom since our facility is the only facility in the Kingdom that is part of the IAEA/WHO Network for Secondary Standard Dosimetry Calibration laboratories. The SSDL Co-60 radiotherapy calibration facility is the first of its kind in the Gulf region. Our services are utilized by over two hundred clients throughout the Kingdom, some of which are from governmental agencies and others are from private sector.
- Upgrading of the Cobalt-60 calibration unit which include installations of
- Optical Distance Indicator, digital field size indication system, Central Beam Axis laser and monitoring system (camera + monitor)
- Establishment of Therapy level calibration capabilities which include Commissioning of the therapy level calibration unit, upgrading of the Cobalt-60 calibration unit and establishment of calibration procedures of ionization chamber used in radiotherapy in terms of absorbed dose to water.
- Establishment of radiation protection and diagnostic radiology calibration capabilities
- RSO successfully demonstrated to the national regulatory body, KA-CARE, our continuous eligibility to maintain our license to operate a radiotherapy facility and a Scientific Research Facility. The RSO has also submitted the necessary paper work to KA-CARE in order to prove our continuous eligibility to maintain our license to operate a Secondary Standard Dosimetry Laboratory, a health physics lab where Leak test are performed and a personal dosimetry Lab.
- Radiation Safety office performed intensive shielding verification for the new nuclear medicine and diagnostic facilities established at King Abdullah Center for Oncology and Liver Diseases.
- Department staff members among the top 10 highest performers for the 2015 international radiotherapy plan challenge
- Staff members were invited panelists to the SunNuclear webinar on achieving conformal plans using different treatment planning systems, September 2015 http://planchallenge.sunnuclear.com/webinars
- Imaging Physics section staff wrote Chapter 15 titled "Devices for Evaluating Imaging Systems" in a book entitled "Nuclear Medicine Physics, A Handbook for Teachers and Students", published by the IAEA in January 2015
- Radiation Physics Oncology staff Co-author of Chapter 11 in a book entitled "Radiation Protection in medical Imaging and Radiation Oncology", CRC Press, Florida, 2015.

The 2015 activities and achievements of the following sections and core facilities of the Biomedical Physics Department are shown in separate reports:

Name of Section	Name of Unit/Core Facility
Radiation Oncology Physics	Clinical Dosimetry and Treatment Planning
Imaging Physics	Gamma Irradiation Facility
Health Physics	Secondary Standard Dosimetry Laboratory
Radiation Biology	Radiation Safety Office
Molecular and Functional Imaging	Business Office

RESEARCH PROJECTS

Listed below are the ongoing research projects in the Biomedical Physics Department.

PROJECT TITLE: Intra-Operative Proton Radiotherapy (IOpRT)

KACST's Advanced and Strategic Technologies Program of the National Comprehensive Plan for Science and Technology Reviewed by the American Association for the Advancement of Science (AAAS) in USA. (Project: 11-BIO1428-20, 24 months, approved for funding, SR 2,000,000, August 2012-Nov. 2015). (Designated a Model Proposal).

INVESTIGATORS: *Belal Moftah (Principal Investigator), Ahmed Ali Basfar, Akram Al-Moussa, Khalid Rababaeh,*

PROGRESS: The project was concluded by the final response to the AAAS Review. Two new 3D polymer Gel compositions were developed and four USPTO patents have been submitted. Publications are ongoing.

PROJECT TITLE: Assessing the Genotypes' Distribution of Genetic Polymorphic Variations and their Impact on the Risk of Radiation Exposure in Saudi Individuals

KACST, National Plan for Science and Technology (# 11-BIO1429-20) ORA/RAC # 2120 003

INVESTIGATORS: *Ghazi Alsbeih, Faisal Abou-Tarboush, Salma Majid, Mohamed Shoukri*

This project has been completed. It has included the required 124 fibroblast cell strains. Clonogenic survival assay was 95% completed and survival curves were generated. Radiosensitivity, characterized by the surviving fraction at 2Gy (SF2) ranged between 0.12 and 0.49 (mean = 0.33, SD = 0.087) indicating wide range of radiosensitivity between Saudi individuals. The mean SF2 divided the cell strains into radiosensitive (61 cases) and normal (63 controls). Genotyping of SNPs have identified the frequency of the studied SNPs in Saudi donors and preliminary statistical analysis showed significant association between SF2 and allelic frequencies of XRCC1 399 G/A and A^{TM} codon 1853 G/A ($P \leq 0.05$). Preliminary GWAs study using CytoScan platform showed significantly higher number of CNVs post-radiation in radiosensitive cells. These results indicate that certain genetic variations are associated with relative decrease in radiosensitivity.

PROJECT TITLE: Role of HPV Infection and Genetic Predisposition in Colorectal, Breast and Head and Neck Cancers in Saudi Arabia

National Science Technology and Innovation Plan (NSTIP) (# 12-MED2945-20) ORA/RAC # 2130 025

INVESTIGATORS: *Ghazi Alsbeih, Medhat Elsebaie, Nasser Alrajhi, Asma Tulbah*

The primary aim of this project is to explore the potential involvement of HPV infection in 200 Head & Neck, 100 Breast and 100 Colorectal Saudi cancer patients. The project also involves testing for the expression level of p16 proteins as marker of HPV infection and prognostic of treatment outcome

and determining the genotype distribution of TP53 codon 72 G/C and HDM2 promoter 309 T/G SNPs genetic predisposing factors to cancer in those patients by comparing with 400 matched controls without cancer.

In the 2-year of this project we have obtained lists of Head & Neck, colorectal and breast cancer patients who were treated at KFSH&RC. We have reviewed medical record and pathological blocks of over 600 patients and had selected the required 400 cases for this project. We have also set up all the required techniques including real-time PCR for HPV integration. DNA was extracted and made available for down-stream experiments. However, the Linear Array HPV Genotyping Test (Roche Diagnostics) failed to detect HPV infection in a cohort of 108 Head & Neck tumors. Therefore, a real-time multiplexed Xpert HPV (Cepheid Company) technique was implemented and a preliminary test using 10 samples revealed 2 HPV-positive cases (Figure 3). Consequently, we are retesting our samples using this more accurate technique to successfully complete the remaining aims of the study.

PROJECT TITLE: Involvement of Genetic Polymorphic Variations and Their Association with HPV Integration in Patients with Head and Neck Cancers
ORA # 2140 026

INVESTIGATORS: *Ghazi Alsbeih, Sharifa Hamed, Aisha Al-Qarni (MSc student, KSU)*

Emerging evidence identify Human Papillomavirus (HPV) as causative agent for squamous cell carcinoma of the Head and Neck (HNSCC) in addition to the well-known cervical and other anogenital tumors. Moreover, HPV-positive HNSCC appears to form separate subgroups among their counterparts with different characteristics and therapeutic response to chemo-radiation treatment. The biology of HPV-positive HNSCC, particularly oropharyngeal cancer, is distinct with p53 degradation, retinoblastoma RB pathway inactivation,(due to E6 and E7 oncoproteins expressions, respectively) and p16 upregulation. By contrast, tobacco-related oropharyngeal cancer is characterized by TP53 mutation and downregulation of CDKN2A (encoding p16). The causative relationship between high-risk (HR) HPVs and cervical carcinoma is well established since the early seventies and had led to the development of the HPV vaccines. By far the HR HPVs 16 & 18 are the most common genotypes involved in cancer worldwide. Thus, HPVs detection and genotyping are expected to gain importance in clinical settings for cancer patients.

HPV infection is common in human and only a minority of patients could HPV integrate into host-genome and cause cancer. Thus genetic predisposition may play a role in HPV-mediated carcinogenesis. Single-nucleotide polymorphisms (SNPs) are the most common genetic variation between human. The TP53 codon 72 (G/C) and HDM2 promoter 309 (T/G) SNPs were suggested to predispose to malignancies. The significance of HPV in Saudi HNSCC and its association with SNPs are still unknown. The aim of this study is to determine the distribution of HPVs infections and its integration in these cancers, its association with immunohistochemical expression of E6 oncoprotein as probable diagnostic marker of active HPV infection, and their potential association with host genetic predisposing SNPs variations in TP53 and HDM2 genes. Paraffin-embedded tumor samples from 100 adult Saudi patients treated with radiation for Head and Neck (particularly oro-pharynx) cancers will be examined. Genetic predisposing SNPs will be determined by comparison with genotypes frequencies in 100 age/gender matched controls without cancer. The gathered information will pave the way to evaluate

the usefulness of implementing HPV vaccines to prevent HPV-mediated cancers and to improve cure rate and reduce mortality, which may render these tumors preventable and curable.

PROJECT TITLE: Potential Role of HPV Infection and Genotype in Saudi Head and Neck Cancers Patients Treated with Radiotherapy
ORA # 2140 027

INVESTIGATORS: *Ghazi Alsbeih, Sharifa Hamed, Wejdan Al-Qahtani (MSc student, KSU)*

Cancer development is a multistep process involving environmental, lifestyle, genetic and possible infectious agents that promote carcinogenic transformation. Viruses cause some of the most important infections for cancer development in humans, second only to tobacco use. Human papillomavirus (HPV) stands out as being implicated in several types of human carcinomas including not only cervix uterine and other anogenital cancers but also subgroup of head and neck cancers as roughly 96%, 60%, and 30% of these malignancies are positive for high risk HPVs. HPV infection is common in human particularly in young age and increase with intimate contact with and without clinical lesions. Its pathological role in cervical and other anogenital cancers is well established and had led to the development of the first HPV anticancer vaccines and advocates are promoting its use to prevent and treat other HPV-mediated cancers.

The involvement of HPV infection in Head & Neck cancers in Saudi patients is unknown. The aim of this retrospective study is to determine the distribution of HPVs infections and genotypes in these cancers, their pathological association with p16 protein expression, suggested as biomarker for HPV-infection and outcome of chemo-radiation therapy. Paraffin-embedded tumor samples from 100 patients treated for Head and Neck (particularly oro-pharynx) cancers will be examined. HPV infection and genotype will be determined using Linear Array HPV Genotyping Test (LA HPV GT; Roche Diagnostics) and p16 protein immunohistochemical staining. The overall significance of this study is to provide health authority with basic experimental information about the relationship between HPV infections in Head & Neck cancer patients. The gathered information will indirectly pave the way to evaluate the usefulness of implementing HPV vaccines to prevent HPV-mediated cancers and to improve cure rate and reduce mortality, which may render these tumors preventable and curable.

PROJECT TITLE: A Non-invasive and Sensitive Molecular Blood Assay to Evaluate Treatment Response/Relapse in Women with Breast Cancer
RAC # 2110 20

CO-INVESTIGATOR: *O. Demirkaya*

Our role as a co-investigator in this project is to investigate the correlation of the molecular blood assay results with the positron emission tomography (PET) and other breast imaging results.

PROJECT TITLE: Building a Web-based Database for Quality Control/Assurance Data in Nuclear Medicine

INVESTIGATORS: *O. Demirkaya, R. AlMazrou, and Rikka Santos*

Currently, daily QC/QA results are saved in Excel sheets (e.g. daily constancy data for dose calibrators and CT numbers) and are not backed up. It is very often the case that these files are saved on an individual technologist's account. When the technologist is absent from work, he or she shares her password with others to have the others access to the file. The quality control tests'

data acquired by medical physicists are saved on the responsible medical physicist's computer or logged on his/her personal computer and cannot be usually accessed by the other medical physicists when s/he is absent from work. This practice is not the most appropriate one given the tools and technology for data collection and archiving at our disposal today. This proposal is the first attempt to centralize the QC/QA data. The successful implementation of this project may facilitate the incorporation of the other modalities. Some major benefits of this project can be enlisted as follows:

- Facilitate for a more efficient and effective quality control and assurance
- Allow data entry from anywhere using a web interface
- Allow the centralization of the data
- Facilitate the access to data for all the collaborators: medical physicist, technologists and QA coordinators in Radiology
- Help the medical physicists to follow the status of nuclear medicine equipment in a more effective and timely manner
    - Allow easy-generation of statistics and reports

Since the department of Radiology is currently completely filmless, a paperless QC/QA record keeping will be the most befitting. Furthermore, the centralization of the quality control data can also facilitate the ACR accreditation of the clinical procedures in nuclear medicine and the future JCIA surveys.

Although the system we developed is currently being used. We will continue adding the other imaging modalities to it.

PROJECT TITLE: Oncological Applications of F-18 Fluorocholine PET/CT; A Prospective Study to Evaluate Its Role in Patients' Management

RAC# 2151003

CO-INVESTIGATOR: *O. Demirkaya*

This is a new project in which a new tracer, F-18 Fluorocholine, will be used in cancer patients. This is a prospective study to investigate the role of the tracer in patient management. The grant proposal submitted to KACCT has been approved for the years 2015–2017. We are currently collecting patients and analyzing patient data.

PROJECT TITLE: Localizing Hypoxic Tumor Volumes for Radiotherapy Treatment Planning

CO-INVESTIGATOR: *O. Demirkaya*

This is another new project in which the use of O-15 in localizing hypoxic tumors will be investigated. A grant proposal has been submitted to KACST and has just being approved. The project has not started yet.

FUTURE RESEARCH DIRECTION

Albeit providing clinical service is our principal responsibility, the department will continue to participate in more research and development projects. The future research directions for each section of Biomedical Physics are indicated in the sectional reports.

PUBLICATIONS

Detailed information of publications of the Biomedical Physics Department for the year 2015 is listed in each section's annual report.

BUSINESS OFFICE

OFFICE COORDINATOR

Eng. Saad Bin Jamaan

STAFF MEMBER

Mr. Mohammed Awad *(Grant Employee)*

The Biomedical Physics Business Office functions are:

- Provide immediate services to customers
- High quality service with low cost
- Shorten cycle time of the product or service
- Systematization of work

BPD BUSINESS OFFICE ACTIVITIES

Customers queries by:

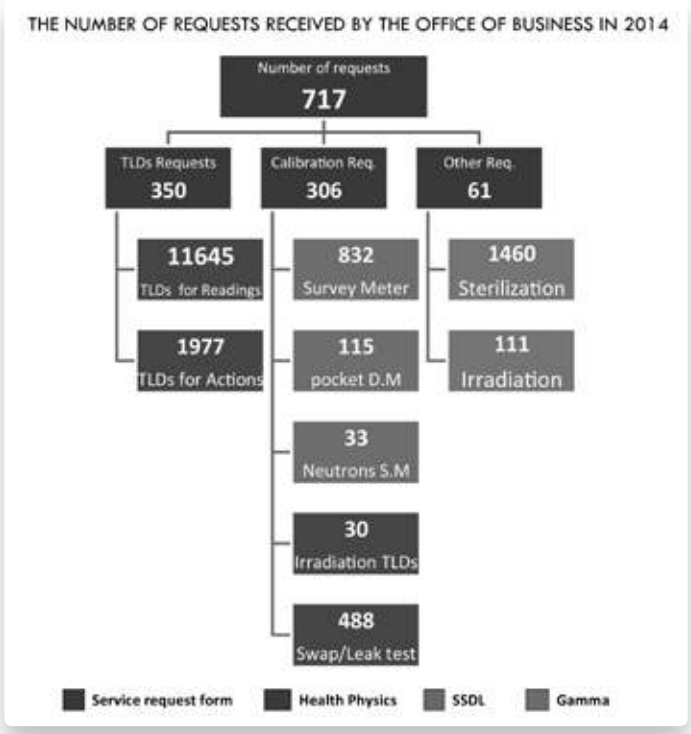
- Phone calls - Fax - Email
- Personal visit
- Transferred by: Secretary, Sections Heads, Department Staff and the Chairman

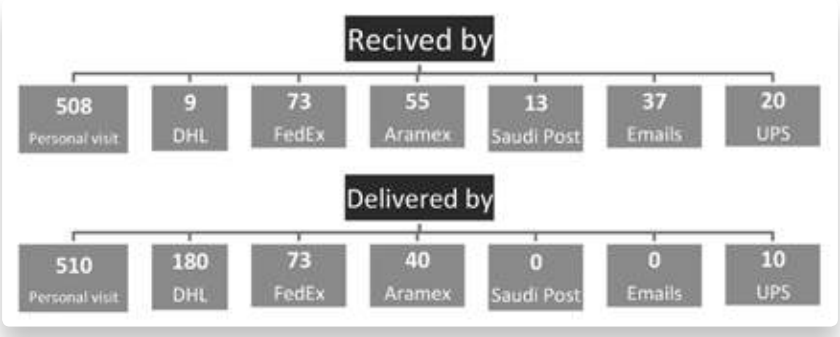
Queries about:

- Biomedical Physics Department Services
- Price qutations
- Invoices
- Devices/ Items Status

Daily activities:

- Checking the SRF with the Items by counting TLDs / devices (serial number / Model) / Other
- Log all information in the receiving log sheet
- Send to and receiving the items from the each BPD sections
- Payment follow up


THE NUMBER OF REQUESTS RECEIVED BY THE OFFICE OF BUSINESS IN 2014
Number of requests
717
TLDs Requests
350
Calibration Req.
306
Other Req.
61
11645
TLDs for Readings
1977
TLDs for Actions
832
Survey Meter
115
pocket D.M
33
Neutrons S.M
30
Irradiation TLDs
488
Swap/Leak test
1460
Sterilization
111
Irradiation
Service request form
Health Physics
SSDL
Gamma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CLINICAL DOSIMETRY AND TREATMENT PLANNING UNIT

HEAD

Waleed Alnajjar, PhD, ABMP, DABR

MEMBERS

Manal Awidh, BSc, CMD *(Grant until May 2015)*
Osama Hassad, BSc, CMD
Arwa Helmi, BSc
Ghadeer Nazer, BSc, CMD
Wedyan Safar, BSc, CMD
Khaled AlQahtani, BSc
Afrah Alsomali, BSc

2015 HAS CONTINUED TO FOLLOW THE 2014 PATTERN OF increased planning volumes and more overall complexity in planning. With new technologies we are able to treat more advanced cancer than in the past but it requires more planning time to achieve an optimum plan. The increase in number of treatment plans are seen primarily in Tomotherapy and Rapid Arc — our most labor intensive and highly technical techniques. This is good for the patient population but difficult for the limited number of qualified dosimetrists we have for planning.

We have streamlined processes and adjusted time frames for start of radiation treatment to allow staff the necessary time to create optimal radiation treatment plans. This was an important step to maintain safety and offer the best outcome for the patients.

Although we worked hard to recruit dosimetrists we were not able to compete in the market and by the end of 2014 we will have lost 3 Certified Medical Dosimetrists. Our staff has decreased by 50% while procedure volumes increased significantly. We are utilizing physics staff to assist in the treatment planning section for the short term. We are also reviewing recruitment packages and retention bonuses. This is a serious issue for the department.

For 2016 our plan remains to increase the number of qualified Medical Dosimetrists. We need to look at not only recruitment but retention plans. In addition there will be as great deal of training and change as we move into the new King Abdullah Cancer Center and Liver Diseases in the second half of the year.

CORE SERVICE ACTIVITIES

ACTIVITIES	2015
Monitor Unit (MU) Calculation/2-Dimensional Contour	4
Total Body Irradiation (TBI) Calculation	60
3-Dimensional CT Treatment Planning	1529
Electron Cut-out Measurement	64
Intensity Modulated Radiation Therapy (IMRT)	39
RapidArc	540
Tomotherapy	243
CyberKnife	76
TLD Dosimetry	5
Intraoperative	68
High Dose-Rate (HDR) Brachytherapy	47
Low Dose-Rate (LDR) Brachytherapy	3
Clinical Consultation	144
TOTAL PROCEDURES	**2876**
PATIENTS	**1480**
MANHOURS	**12166**

*Manhours calculated by taking the average number of Dosimetrists/ Medical Physicists on duty(5) working on the above procedures for an average of 40 hours per week for 52 weeks of the year. This figure approximately accounts for Annual Leave, Over-time and also the limited times when we have a lull in patients numbers (Eid, etc).

TRAINING AND EDUCATION ACTIVITIES

We continue to provide training in clinical dosimetry and have engaged the University of Southern Illinois, USA to assist in providing the education required for the Medical Dosimetry Certification Board – the only internationally recognized medical dosimetry certification. We are currently reviewing the contract and plan to implement this formal program in the Fall 2015. We are committed to the highest standards of dosimetry and have an entire staff of Certified Dosimetrists. This program is an effort to address the shortage of Certified Medical Dosimetrists available for hire.

Additionally, the Dosimetry staff continues to teach treatment planning to physics undergraduate and graduate students from different universities within the Kingdom and also to individuals from ARASIA member-countries. We also continue to work as a greater team with our Radiation Physics Section colleagues to provide mutual training in the different areas related to clinical dosimetry.

STAFFING

Due to our continuing staff shortage, made worse by the difficulty in recruiting Certified Medical Dosimetrists and the loss of three dosimetrists, we continue to rely on our colleagues from the Radiation Physics Section as well as additional physics graduate Grant Employees to assist us in our workload.

The Dosimetry Unit hopes to recruit new senior staff in 2014 to enable increased participation in research activities and production of scientific papers based around our knowledge of advanced radiation treatment modalities

GAMMA IRRADIATION FACILITY

OFFICE COORDINATOR
Akram Al-Moussa, MSc

STAFF MEMBER
Saad Bin-Jamaan, BSc
Edilberto Delos Reyes

THE GAMMA IRRADIATION FACILITY (GIF) IS ONE OF THE CORE facilities of the Biomedical Physics Department in the Research Centre. The Facility is ISO 9001-2000 certified. It operates with three primary goals, namely: (1) to sterilize health care products for the needs of the KFSH&RC departments, and to provide this service commercially to health care products manufacturers all over the Kingdom; (2) to transfer radiation-processing technology to the country encouraging new in industries; and (3) to provide a high activity radioactive source for variety of research projects.

STAFF OF THE FACILITY

- One Engineer, Head of the facility, dosimetrist
- One operator
- One Technician

CORE SERVICE ACTIVITIES

The activities of the Gamma Irradiation Facility are:

- Continued to provide sterilization for hospital needs (Bone bank, Cell Biology, Comparison medicine and supplies of ART laboratory and biomedical research section).
- The visit of the GIF twice a year is fixed to be a part of academic course, college of food science and agriculture, King Saud University.
- Renewal of ISO certification, auditing is going successfully without any major or minor comment, to keep always highest standards (this procedure has to be done annually and regularly otherwise we lose our ISO certificate).
- Dosimetry laboratory in GIF is working in cooperation with KACST on development of the 3 D Gel compositions. Upgrade of the laser scanner for the 3 D Gel is done. The new updated system will allow putting the 3 D gel verification system on the service for the KFSH&RC and other institutes that are using radiation therapy but they don't have the laser scanner and the 3 D technology.
- Visitors of the KFSH&RC visiting the facility every year, since it could be the only facility in the world attached to a hospital

GAMMA RAY STERILIZATION

The Gamma Irradiation Facility has continued to provide sterilization services for the Hospital departments and other institutions on a fee for service basis. Sterilization of different items such as pharmaceuticals for Tabuk Company and Riyadh Pharma Company and some frequent customers, such as National Guard Hospital.

The staff of the facility is trying to develop services to follow the latest technology and stay in competition with modern-day irradiators.

New products can be manufactured here in KFSH&RC if we achieve the new technology development, which is the hydrogel wound dressing; a special composition of the said product was developed in GIF laboratory.

Replacement of the radioactive source installed in 2002 and has 12 years old with electron beam technology will help in increasing the services of the facility and its income.

- Gamma irradiation Facility started to provide a very valuable and priceless new service, it is the sterilization of bones for the BONE BANK in KFSH&RC. These bones can only be sterilized with Gamma radiation.The Facility has one of the best dosimetry laboratories in the region with annual inter-comparison program with National laboratory of RISO, DENMARK.
- GIF also calibrates the Gamma Cells in KACST and they would request for our help in radiation dosimetry from time to time.

HEALTH PHYSICS SECTION

HEAD

Fareed Mahyoub, MSc, MIPEM

STAFF MEMBER

Celestino S. Lagarde, BSc

Ibrahim Al-Gain, MSc, MIPEM

Shaima Alshora, BSc *(RC Grant)*

Huda Al-Ghamdi, BSc *(RC Grant)*

Noor Aleidan, BSc *(RC Grant)*

THE HEALTH PHYSICS SECTION IS COMMITTED TO ITS MISSION OF limiting the risks of exposures to patients, staff and members of the public. It is recognized by the International Atomic Energy Agency (IAEA) as a center for training in radiation protection and measurement. Its personnel radiation dose monitoring service is accredited by IAEA, thus meeting the international high standards for radiation protection. The Section maintains a thermoluminescent dosimetry (TLD) Laboratory that is licensed by the King Abdulaziz City for Science & Technology (KACST) making it the only laboratory in the Kingdom to meet national regulatory requirements. Leak tests for private companies were also provided by the section.

HEALTH PHYSICS ACTIVITIES

The table on the right summarizes the accomplishments made by the Health Physics Section for year 2014 in providing services to the KFSH&RC, to other facilities in the Kingdom of Saudi Arabia and surrounding countries in the Gulf region.

Task Descriptions	Quantity
No. of Radiation workers monitored for occupational doses	5712
No. of Personnel Radiation Monitoring performed	25672
Patients surveyed for radiation level	255
Patients rooms surveyed for radiation level	255
Patients rooms decontaminated	255
Leak test for sealed sources and radiation producing equipment	
TLD badges irradiated for quality control of TLD readers of outside facilities	55
Internal TLD badges irradiated for quality control of TLD readers and users	25672
Consultative advice provided	4
Training courses & educational lectures provided	8

IMAGING PHYSICS SECTION

HEAD

Omer Demirkaya, PhD, DABSNM

STAFF MEMBERS

Ibrahim Al-Anazi, MSc, ABHP, ABMP

Refaat Y. Al-Mazrou, MSc, FIPEM

Adnan Z. Al-Watban, PhD, FIPEM

Huda Musallay, B.S

THE IMAGING PHYSICS SECTION HAS CONTINUED TO PROVIDE clinical medical physics services to the departments of Radiology, OR, Dentistry, Cath Lab and Radiotherapy of the KFSH&RC (Riyadh); the department of Radiology of the King Fahad National Children's Cancer Centre & Research (KFNCCC&R), Royal Palace satellite clinics and mobile vans. Imaging modalities served by our staff include: dental x-ray, general digital radiography (DR), portable conventional and digital radiography, bone densitometry, computed radiography (CR), conventional and digital fluoroscopy, angiography, conventional and digital mammography, cath lab, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, positron emission tomography (PET)/CT, gamma camera and SPECT/CT systems.

CLINICAL SERVICE

The clinical services make up the major portion of our work. Most of the clinical services provided fall under the broad category of imaging equipment acquisition, implementation and proper operation. The process starts with request for proposal (RFP) preparation for the purchase of diagnostic imaging equipment and ending with implementation of a technologist-oriented quality control monitoring program supervised by a medical physicist. Maintenance of many of our quality control programs; in addition, to solving day-to-day problems, requires section staff to perform (depending on the modality being tested) quarterly, semi-annual and/or annual testing, calibrations of imaging equipment and support devices such as dose calibrators, evaluating and implementing new imaging technologies, assisting with clinical trials, and performing patient radiation exposure/image quality optimizations.

The amount of the clinical work has been increasing and will increase further with the purchase of new imaging equipment in the department of Radiology and in the King Abdullah Cancer Center and Liver Disease (KACC&LD). We have also performed the shielding calculations and verifications for the new imaging areas in the King Abdullah Cancer Center and Liver Disease (KACC&LD).

TRAINING AND EDUCATION

Section staff is also involved in numerous continuing education training programs often in collaboration with regional associations/local societies to promote the discipline of diagnostic radiologic and nuclear medicine physics. Our contribution as a section has been significant to the upcoming ICRM2016 conference in which we expect more than 300 attendees. We have established a residency program in Nuclear Medicine Physics which will start in couple months, in collaboration with the International Atomic Energy Agency (IAEA). Our section staff also contributed to the training course for the Nuclear Medicine fellows in our institution. The section staff has also contributed to the Medical Physics and Radiation Protection training course given to the technologists and medical physicists from the Ministry of Health. Lastly, our section staff conducted a workshop on Gamma Camera Quality Control at the 6th Gulf Nuclear Medicine conference in Doha, Qatar.

RESEARCH

We have several ongoing research and development projects and participated as a co-investigator in two new research projects which have been submitted to KACST.

PROJECT TITLE: A Non-invasive and Sensitive Molecular Blood Assay to Evaluate Treatment Response/Relapse in Women with Breast Cancer
RAC # 2110 20

CO-INVESTIGATOR: *O. Demirkaya*

Our role as a co-investigator in this project is to investigate the correlation of the molecular blood assay results with the positron emission tomography (PET) and other breast imaging results.

PROJECT TITLE: Building a Web-based Database for Quality Control/Assurance Data in Nuclear Medicine

INVESTIGATORS: *O. Demirkaya, R. AlMazrou, and Rikka Santos*

Currently, daily QC/QA results are saved in Excel sheets (e.g. daily constancy data for dose calibrators and CT numbers) and are not backed up. It is very often the case that these files are saved on an individual technologist's account.

When the technologist is absent from work, he or she shares her password with others to have the others access to the file. The quality control tests' data acquired by medical physicists are saved on the responsible medical physicist's computer or logged on his/her personal computer and cannot be usually accessed by the other medical physicists when s/he is absent from work. This practice is not the most appropriate one given the tools and technology for data collection and archiving at our disposal today. This proposal is the first attempt to centralize the QC/QA data. The successful implementation of this project may facilitate the incorporation of the other modalities. Some major benefits of this project can be enlisted as follows:

- Facilitate for a more efficient and effective quality control and assurance
- Allow data entry from anywhere using a web interface
- Allow the centralization of the data
- Facilitate the access to data for all the collaborators: medical physicist, technologists and QA coordinators in Radiology
- Help the medical physicists to follow the status of nuclear medicine equipment in a more effective and timely manner
- Allow easy-generation of statistics and reports

Since the department of Radiology is currently completely filmless, a paperless QC/QA record keeping will be the most befitting. Furthermore, the centralization of the quality control data can also facilitate the ACR accreditation of the clinical procedures in nuclear medicine and the future JCIA surveys.

Although the system we developed is currently being used. We will continue adding the other imaging modalities to it.

PROJECT TITLE: Oncological Applications of F-18 Fluorocholine PET/CT; A Prospective Study to Evaluate its Role in Patients' Management
RAC# 2151003

CO-INVESTIGATOR: *O. Demirkaya*

This is a new project in which a new tracer, F-18 Fluorocholine, will be used in cancer patients. This is a prospective study to investigate the role of the tracer in patient management. The grant proposal submitted to KACCT has been approved for the years 2015–2017. We are currently collecting patients and analyzing patient data.

PROJECT TITLE: Localizing Hypoxic Tumor Volumes for Radiotherapy Treatment Planning

CO-INVESTIGATOR: *O. Demirkaya*

This is another new project in which the use of O-15 in localizing hypoxic tumors will be investigated. A grant proposal has been submitted to KACST and has just being approved. The project has not started yet.

FUTURE DIRECTIONS

Although providing clinical service is our primary responsibility, the section is striving to initiate and participate in more research and development projects. Several ongoing and new research activities are underway in the Section. The first project is directed toward PET/CT applications in medicine where imaging applications are being developed to assist radiologists in improving their clinical protocols to improve diagnostic detection of malignant disease via the use of image analysis and quantification techniques.

The Nuclear Medicine Section of the department of Radiology has been providing a molecular

radiotherapy (MRT) services such as I-131, Lu-177 and Yttrium-90 (TheraSphere). There is an unmet need for an internal dosimetry calculation service for an effective and safe treatment of patients. The dosimetry calculation allows the optimization of the dose delivered to the target tissue and minimization of the dose to normal or high risk organs such as lungs. The dosimetry service is a multifaceted and multidisciplinary service involving nuclear medicine physicists, nuclear medicine physicians, technologists and radiopharmacists. One of the future plans is to establish a clinical molecular therapy dosimetry service in collaboration with the Nuclear Medicine Section in the department of Radiology. We have already spent some time investigating the requirements and the needs for such a service.

One of the recent achievements of our department was to establish a medical physics residency program in Radiotherapy Physics fully supported/approved by the International Atomic Energy Agency (IAEA). A residency program in Nuclear Medicine Physics has also been established under the section supported and approved by the IAEA with the support of the King Abdullah City for Atomic and Renewable Energy (KA CARE).

MOLECULAR AND FUNCTIONAL IMAGING

HEAD
Rafat Mohtasib, PhD

PRESENTLY IN ITS SEVENTH YEAR OF EXISTENCE, THE MOLECULAR and Functional Imaging (MFI) group has pursued both intramural and extramural funding in congruence with its strategic plan.

We have two funded projects through KACST, titled "Advanced magnetic resonance imaging (MRI) for patients with mild cognitive impairment (MCI) and patients with Alzheimer's disease (AD). (Reviewed by the American Association for the advancement of Science (AAAS) was highly recommended for funding from KACST). The other funded research project tiled "Analysis of Neuroanatomic and Neurofunctional Substrates in Autism Spectrum Disorder". In addition to our ongoing funded research project from SABIC titled "Anatomical and functional substrates in ASD", (in collaboration with the University of Leuven, Healthcare Belgium and the Center for Autism Research at KFSH&RC).

We have the following six non-funded projects:

1. Assessment & Development of Functional Imaging Protocols In Epilepsy.
2. Establishing fMRI protocol for clinical use: Comparisons of Different Language Paradigms in Arabic Speakers.
3. Normal Sonographic Dimensions of Spleen and kidney for Children in KFSH&RC.
4. Training parent to conduct Discrete Trial Teaching strategy for their children with Autism Spectrum Disorder (ASD) At Center For Autism Research (CFAR), Riyadh, Saudi Arabia.
5. The Reliability of shear-wave elastography in distinguishing between breast lesions.
6. Establishing fMRI protocol for clinical use: Comparisons of Different Language Paradigms in Arabic Speakers.

RADIATION BIOLOGY SECTION

HEAD

Ghazi Alsbeih, PhD

MEMBERS

Krishnanad Mishra, PhD *(Grant, started October 2015)*
Najla Al-Harbi, BSc
Muneera Al-Buhairi, BSc
Khaled Al-Hadyan, MSc *(on PhD study leave)*
Sarah Bin Judia *(formerly Al-Qahtani)*, BSc
Sara El-Ewisy, BSc *(Grant)*
Nikki Venturina, BSc *(Grant)*
Jenelyn Castro, BSN, RN, *(Grant)*

THE DISCIPLINE OF RADIOBIOLOGY PROVIDES THE BIOLOGICAL BASIS of the many uses of radiation in medical and allied health professions. It is devoted to study the interaction between radiation and living materials and organisms. The aim is to better understand and master this tool in health and medicine and therefore, to improve its beneficial effects and avoid its hazardous potential.

RESEARCH PROJECTS

PROJECT TITLE: Assessing the Genotypes' Distribution of Genetic Polymorphic Variations and their Impact on the Risk of Radiation Exposure in Saudi Individuals
KACST, National Plan for Science and Technology (# 11-BIO1429-20)
ORA/RAC # 2120 003

INVESTIGATORS: *Ghazi Alsbeih, Faisal Abou-Tarboush, Salma Majid, Mohamed Shoukri*

This project has been completed. It has included the required 124 fibroblast cell strains. Clonogenic survival assay was 95% completed and survival curves were generated (Figure 1). Radiosensitivity, characterized by the surviving fraction at 2Gy (SF2) ranged between 0.12 and 0.49 (mean = 0.33, SD = 0.087) indicating wide range of radiosensitivity between Saudi individuals. The mean SF2 divided the cell strains into radiosensitive (61 cases) and normal (63 controls). Genotyping of SNPs have identified the frequency of the studied SNPs in Saudi donors and preliminary statistical analysis showed significant association between SF2 and allelic frequencies of XRCC1 399 G/A and ATM codon 1853 G/A ($P \leq 0.05$). Preliminary GWAs study using CytoScan platform showed significantly higher number of CNVs post-radiation in radiosensitive cells (Figure 2). These results indicate that certain genetic variations are associated with relative decrease in radiosensitivity.

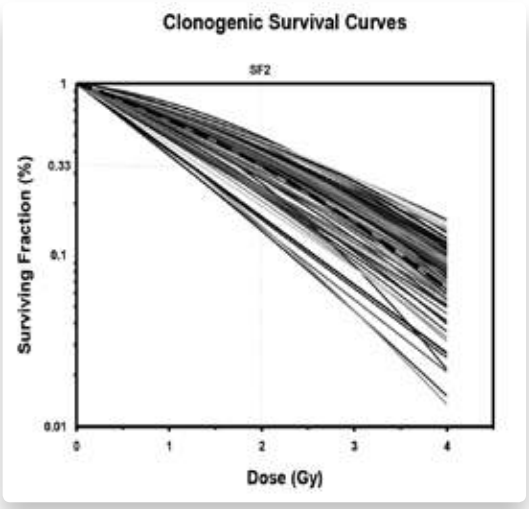


Figure 1: Clonogenic survival curves of the 124 fibroblast cell strains fitted to the Linear-Quadratic model. The mean SF2 of 0.33 (dashed black curve) divided the cell strains to normally sensitive (above the dashed curve) and radiosensitive (below the dashed curve).

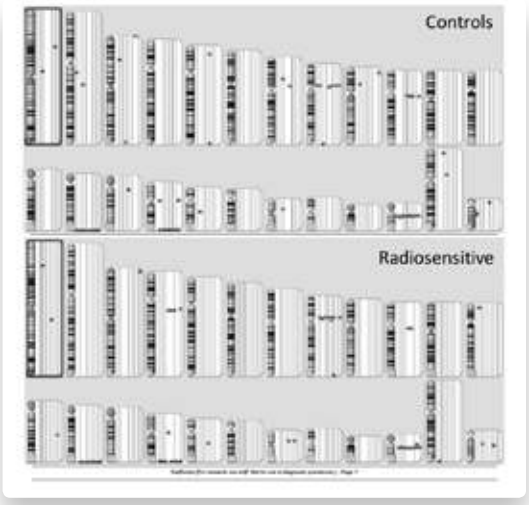


Figure 2: Karyoview of Cytoscan HD arrays showing copy number variation (CNVs) between 9 normal (Control) and 9 radiosensitive cell strains. Each colored vertical line represents different cell strains. Blue arrow-heads represent gains while red arrow-heads represent losses.

PROJECT TITLE: Role of HPV Infection and Genetic Predisposition in Colorectal, Breast and Head and Neck Cancers in Saudi Arabia
National Science Technology and Innovation Plan (NSTIP) (# 12-MED2945-20)
ORA/RAC # 2130 025

INVESTIGATORS: *Ghazi Alsbeih, Medhat Elsebaie, Nasser Alrajhi, Asma Tulbah*

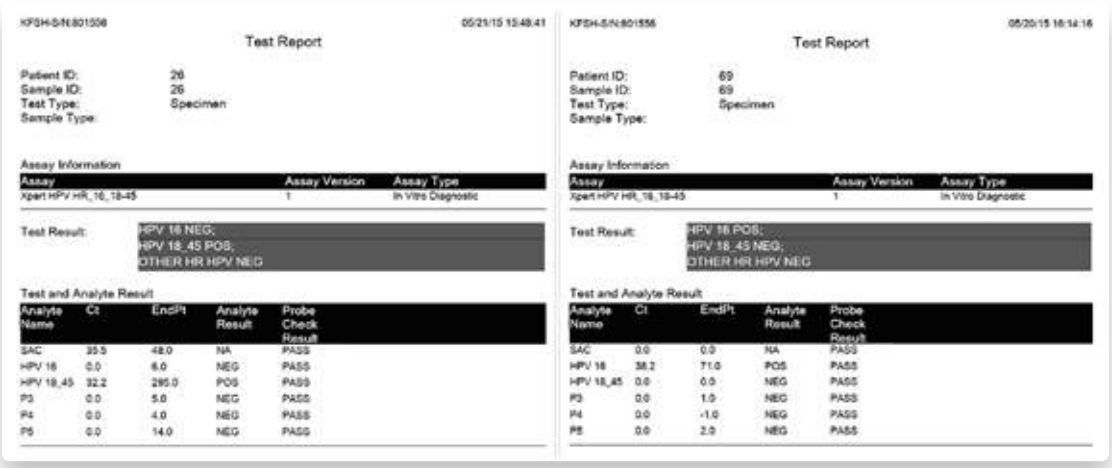
The primary aim of this project is to explore the potential involvement of HPV infection in 200 Head & Neck, 100 Breast and 100 Colorectal Saudi cancer patients. The project also involves testing for the expression level of p16 proteins as marker of HPV infection and prognostic of treatment outcome and determining the genotype distribution of TP53 codon 72 G/C and HDM2 promoter 309 T/G SNPs genetic predisposing factors to cancer in those patients by comparing with 400 matched controls without cancer.

In the 2-year of this project we have obtained lists of Head & Neck, colorectal and breast cancer patients who were treated at KFSH&RC. We have reviewed medical record and pathological blocks of over 600 patients and had selected the required 400 cases for this project. We have also set up all the required techniques including real-time PCR for HPV integration. DNA was extracted and made available for down-stream experiments. However, the Linear Array HPV Genotyping Test (Roche Diagnostics) failed to detect HPV infection in a cohort of 108 Head & Neck tumors. Therefore, a real-time multiplexed Xpert HPV (Cepheid Company) technique was implemented and a preliminary test using 10 samples revealed 2 HPV-positive cases (Figure 3). Consequently, we are retesting our samples using this more accurate technique to successfully complete the remaining aims of the study.

PROJECT TITLE: Involvement of Genetic Polymorphic Variations and Their Association with HPV Integration in Patients with Head and Neck Cancers
ORA# 2140 026

INVESTIGATORS: *Ghazi Alsbeih, Sharifa Hamed, Aisha Al-Qarni (MSc student, KSU)*

Emerging evidence identify Human Papillomavirus (HPV) as causative agent for squamous cell carcinoma of the Head and Neck (HNSCC) in addition to the well-known cervical and other anogenital tumors. Moreover, HPV-positive HNSCC appears to form separate subgroups among their counterparts with different characteristics



Test Report

Patient ID: 28
Sample ID: 26
Test Type:
Sample Type: Specimen

Assay Information

Assay	Assay Version	Assay Type
Xpert HPV HR_16_18-45	1	In Vitro Diagnostic

Test Result: HPV 16 NEG; HPV 18_45 POS; OTHER HR HPV NEG

Test and Analyte Result

Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result
SAC	35.5	48.0	NA	PASS
HPV 16	0.0	6.0	NEG	PASS
HPV 18_45	32.2	295.0	POS	PASS
P3	0.0	5.0	NEG	PASS
P4	0.0	4.0	NEG	PASS
P5	0.0	14.0	NEG	PASS

Test Report

Patient ID: 69
Sample ID: 69
Test Type:
Sample Type: Specimen

Assay Information

Assay	Assay Version	Assay Type
Xpert HPV HR_16_18-45	1	In Vitro Diagnostic

Test Result: HPV 16 POS; HPV 18_45 NEG; OTHER HR HPV NEG

Test and Analyte Result

Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result
SAC	0.0	0.0	NA	PASS
HPV 16	38.2	71.0	POS	PASS
HPV 18_45	0.0	0.0	NEG	PASS
P3	0.0	1.0	NEG	PASS
P4	0.0	-1.0	NEG	PASS
P5	0.0	2.0	NEG	PASS

Figure 3: Snapshot of results for 2 H&N samples that were positive for HPV infection.

and therapeutic response to chemo-radiation treatment. The biology of HPV-positive HNSCC, particularly oropharyngeal cancer, is distinct with p53 degradation, retinoblastoma RB pathway inactivation,(due to E6 and E7 oncoproteins expressions, respectively) and p16 upregulation. By contrast, tobacco-related oropharyngeal cancer is characterized by *TP53* mutation and downregulation of CDKN2A (encoding p16). The causative relationship between high-risk (HR) HPVs and cervical carcinoma is well established since the early seventies and had led to the development of the HPV vaccines. By far the HR HPVs 16 & 18 are the most common genotypes involved in cancer worldwide. Thus, HPVs detection and genotyping are expected to gain importance in clinical settings for cancer patients.

HPV infection is common in human and only a minority of patients could HPV integrate into host-genome and cause cancer. Thus genetic predisposition may play a role in HPV-mediated carcinogenesis. Single-nucleotide polymorphisms (SNPs) are the most common genetic variation between human. The *TP53* codon 72 (G/C) and HDM2 promoter 309 (T/G) SNPs were suggested to predispose to malignancies. The significance of HPV in Saudi HNSCC and its association with SNPs are still unknown. The aim of this study is to determine the distribution of HPVs infections and its integration in these cancers, its association with immunohistochemical expression of E6 oncoprotein as probable diagnostic marker of active HPV infection, and their potential association with host genetic predisposing SNPs variations in *TP53* and *HDM2* genes. Paraffin-embedded tumor samples from 100 adult Saudi patients treated with radiation for Head and Neck (particularly oro-pharynx) cancers will be examined. Genetic predisposing SNPs will be determined by comparison with genotypes frequencies in 100 age/gender matched controls without cancer. The gathered information will pave the way to evaluate the usefulness of implementing HPV vaccines to prevent HPV-mediated cancers and to improve cure rate and reduce mortality, which may render these tumors preventable and curable.

PROJECT TITLE: Potential Role of HPV Infection and Genotype in Saudi Head and Neck Cancers Patients Treated with Radiotherapy
ORA # 2140 027

INVESTIGATORS: *Ghazi Alsbeih, Sharifa Hamed, Wejdan Al-Qahtani (MSc student, KSU)*

Cancer development is a multistep process involving environmental, lifestyle, genetic and possible infectious agents that promote carcinogenic transformation. Viruses cause some of the most important infections for cancer development in humans, second only to tobacco use. Human papillomavirus (HPV) stands out as being implicated in several types of human carcinomas including not only cervix uterine and other anogenital cancers but also subgroup of head and neck cancers as roughly 96%, 60%, and 30% of these malignancies are positive for high risk HPVs. HPV infection is common in human particularly in young age and increase with intimate contact with and without clinical lesions. Its pathological role in cervical and other anogenital cancers is well established and had led to the development of the first HPV anticancer vaccines and advocates are promoting its use to prevent and treat other HPV-mediated cancers.

The involvement of HPV infection in Head & Neck cancers in Saudi patients is unknown. The aim of this retrospective study is to determine the distribution of HPVs infections and genotypes in these cancers, their pathological association with p16 protein expression, suggested as biomarker for HPV-infection and outcome of

chemo-radiation therapy. Paraffin-embedded tumor samples from 100 patients treated for Head and Neck (particularly oro-pharynx) cancers will be examined. HPV infection and genotype will be determined using Linear Array HPV Genotyping Test (LA HPV GT; Roche Diagnostics) and p16 protein immunohistochemical staining. The overall significance of this study is to provide health authority with basic experimental information about the relationship between HPV infections in Head & Neck cancer patients. The gathered information will indirectly pave the way to evaluate the usefulness of implementing HPV vaccines to prevent HPV-mediated cancers and to improve cure rate and reduce mortality, which may render these tumors preventable and curable.

SELECTED ACHIEVEMENTS 2015

1. Excellent Poster Award, International Congress on Radiation Research (ICRR), Kyoto, Japan 25-29 May 2015.
2. Expert lecturer, IAEA Regional Training Course on Radiobiology for Radiation Oncologists, Technical Cooperation Project RAF/6/045. 2-6 November 2015. Khartoum, Sudan.

PEER REVIEWED PUBLICATIONS THE LAST 3-YEARS

- Ghazi Alsbeih. Editorial: HPV-associated cancers: Socio-economic disparities and vaccination. *Front Oncol*. 2015 Oct 13;5:223. doi: 10.3389/fonc.2015.00223. eCollection 2015.
- Ala-Eddin Al Moustafa, Rana Al-Awadhi, Nabiha Missaoui, Ishag Adam, Raika Durusoy, Lina Ghabreau, Nizar Akil, Hussain Gadelkarim Ahmed, Amber Yasmeen & Ghazi Alsbeih. Human Papillomaviruses-Related Cancers: Presence and Prevention Strategies in the Middle-East and North African Regions. *Hum Vaccin Immunother*. 2014 Jul;10(7):1812-21. doi: 10.4161/hv.28742. Review. PMID: 24787388.
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RADIATION ONCOLOGY PHYSICS SECTION

HEAD

Belal Moftah, PhD, FCCPM

MEMBERS

Al-Delaijan, Saad, MSc
Al-Kafi, Mohd Abdullah, MSc
Al-Mohammed, Huda, PhD *(until May 2015)*
Al-Najjar, Waleed, PhD, DABR, ABMP
Al-Selham, Hind, MSc
Al-Zorkany, Faisal, MSc
Ashmeg, Sarah, BSc *(on study leave)*
Hassan, Zeinab, PhD *(until October 2015)*
Hussain, Mohamed Abrar, PhD, DABR *(on leave)*
Mahyoub, Fareed, MSc, MIPEM
Mwidu, Umar, MSc
Nobah, Ahmed, MSc, DABR
Santos, Rikka Maureen, MSc
Shehadah, Mamoun, MSc, DABR
Wadi-Ramahi, Shada PhD, DABR

OUR RADIATION ONCOLOGY PHYSICS TEAM CONTINUES TO provide a distinguished clinical service and scientific contribution on five major radiotherapy treatment modalities namely, TomoTherapy, CyberKnife, TrueBeam, Nucletron HDR, Mobetron and Intrabeam. The calibration of our machines have been audited but the Imaging and Radiation Oncology Center (IROC) of the MD Anderson Cancer Center, Tx. Results of all modalities (photons/electrons) was as expected.

The Clinical Dosimetry and Treatment Planning unit of the Radiation Oncology Physics Section has continued to perform quality radiation treatment plans and dosimetric calculations for a wide variety of malignant cancers and benign diseases.

One member of our Radiation Oncology Physics team, Mr. Umar Mwidu, passed the American Board of Radiology board certification exams in 2015. One of the section members, Dr. Shada Wadi-Ramahi, passed the 10-year required maintenance of certification exam of the ABR. Two members, Mr. Ahmad Nobah and Dr. Shada Wadi-Ramahi, participated in the AAMD 2015 Plan Challenge, and their submitted plans were ranked number 8 and number 5, respectively out of 250 plans.

During this reporting year, the Section organized a symposium and workshops entitled "MRI: Basics and Applications in Radiotherapy and Diagnostic Imaging", held 24-26 February 2015. The event host 3 international speakers and 2 local.

The Radiation Oncology Physics staff evaluated the shielding design of the brachytherapy unit at KAOC&LD. Our staff members were also involved in the training of 5 International Atomic Energy Agency (IAEA) residents.

Efforts on the section level continue for retention and for hiring of qualified staff. Training of potential staff members of Saudi nationality has also continued especially in the Clinical Dosimetry and Treatment Planning unit.

TEACHING AND TRAINING ACTIVITIES

The Radiation Oncology Section plays a very active role at the national and international level to enhance the training of physics and physics-related specialties in the health care industry. The section continuously receives trainees from universities, Ministry of Health and other countries to provide high quality training.

- All members of the section taught and trained in a training course for 100 employees of the Ministry of Health with a comprehensive course on Medical Physics and Radiation Protection Training Course including hands-on workshops. The attendees were divided into 4 groups of 25 and each group completed 5-weeks of training. The course started in De 2014 and concluded by May 2015.
- The residents of the first "IAEA/ARASIA Regional Residency Training Program for Medical Physicists in Radiation Oncology at KFSH&RC, have finished their required training and passed two written and one oral exam. The exams were administered by two local faculty and one external (Canadian) faculty. The final exam took place in February 2015.
- Starting a residency program in Nuclear Medicine Physics which is supported by the IAEA and the King Abdullah City for Atomic and Renewable Energy (KACARE) this year and is under review.
- Training of two Al-Razi Summer program students (26/7 – 20/8, 2015).
- Two members of the section, Mr. Ahmad Nobah and Dr. Shada Wadi-Ramahi, were invited to be speakers and panelists at a webinar hosted by Sun Nuclear on using treatment planning systems for better planning, Oct 1st, 2015. http://planchallenge.sunnuclear.com/webinars

INVITED TALKS AT SCIENTIFIC EVENTS

Invited talks are held at a prestigious level because the speaker is recognized to have expertise that is sought after. In 2015, the section participated in invited talks and helped disseminating science and knowledge on the local, regional and international level through the following four activities.

- Dr. Shada Wadi-Ramahi was invited to give a talk entitled "Failure Mode and Effects Analysis (FMEA) and its Application in Medicine" at the King Fahad Medical City conference eon Physics and Engineering in Medicine, Oct 11th – 15th 2015, Riyadh, KSA.
- Dr. Shada Wadi-Ramahi was invited to give a talk entitled "FMEA in HDR brachytherapy" at the Medical Physics Section of the Radiation Oncology Department of the Rush University Medical Center, Oct 22nd 2015, Chicago, USA.
- Dr. Shada Wadi-Ramahi was invited to give a talk entitled "Radiation Therapy: An Image-based therapeutic approach" at the First Radiology Week at Sulaiman Al-Habeeb ALrayan hospital, Nov 3 2015, Riyadh KSA
- Dr. Shada Wadi-Ramahi was invited to be a speaker at the Best of ASTRO (BOA) conference in Sulaymaniah, Iraq, Dec 9th – 12th. Pre-conference activities included a day and a half of physics lectures and hands-n workshop on TRS-

398 and brachytherapy source measurement. The BOA conference included presenting the top ranked physics abstracts at the ASTRO followed with a panel discussion.

RESEARCH PROJECTS

PROJECT TITLE: "Intra-Operative Proton Radiotherapy (IOpRT)

PROGRESS: This project was concluded in November 2015. Publications are ongoing.

PUBLICATIONS

BOOKS AND BOOK CHAPTERS

- Shada Wadi-Ramahi co-authored Chapter 11 in a book entitled "Radiation Protection in medical Imaging and Radiation Oncology", CRC Press, Florida, 2015. ISBN: 978-1-4822-4537-0.

PUBLICATIONS IN REFEREED JOURNALS

- Saad Aldelaijan, Faisal Alzorkany, Belal Moftah, Ivan Buzurovic, Jan Seuntjens, Nada Tomic, Slobodan Devic, Use of a control film piece in radiochromic film dosimetry, Physica Medica: *European Journal of Medical Physics*, in Press (2015). http://www.sciencedirect.com/science/article/pii/S1120179715010467.
- M Abdullah Al Kafi, Umar M Mwidu, Belal Moftah, Continuous versus step-by-step scanning mode of a novel 3D scanner for CyberKnife measurements, *Applied Radiation and Isotopes*, 105 (2015) 88-91. http://www.sciencedirect.com/science/article/pii/S0969804315301019.
- M.W. Hegazy, R.I. Mahmood, I.A. Al-Badawi, B. Moftah, H. AlHusaini, Radiotherapy Dose Escalation with Concurrent chemotherapy in Locally Advanced Cervix Cancer is feasible, *Clinical and Translational Oncology*, July 10, 2015, DOI: 10.1007/s12094-015-1336-5, http://rd.springer.com/article/10.1007/s12094-015-1336-5#.
- Belal Moftah, Saad Aldelaijan, Mamoun Shehadeh, Faisal Alzorkany, Faisal Alrumayan, Ghazi Alsbeih, Mohammad Alshabanah, Jan Seuntjens, and Slobodan Devic, A radiochromic film-based dose monitoring system for radiobiological experiments using low energy proton beams, submitted to *Physics in Medicine and Biology* (2015).
- S. Asgharizadeh, H. Bekerat, A. Syme, S. Aldelaijan, F. DeBlois, T. Vuong, M. Evans, J.Seuntjens, S. Devic, "Radiochromic film-based quality assurance for CT-based high-dose-rate brachytherapy," *Brachytherapy*, 14(4):578-85 (2015). http://www.brachyjournal.com/article/S1538-4721(15)00215-9/abstract.
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- Ahmad Nobah, Mohammed Mohiuddin, Slobodan Devic, Belal Moftah, Effective Spatially Fractionated GRID Radiation Treatment Planning for a Passive Grid Block, *Br J Radiol* 2015;88:20140363. DOI: http://dx.doi.org/10.1259/bjr.20140363.

PRESENTATIONS AT CONFERENCES AND MEETINGS

- B. Moftah, S. Aldelaijan, M. Shehadeh, F. Alzorkani, G. Alsbeih, J. Seuntjens, S. Devic. "Radiochromic Film Based Dose Calibration and Monitoring for Radiobiological Experiments using Low Energy Proton Beams," World Congress on Medical Physics and Biomedical Engineering (WC 2015), Toronto, Canada (2015).

- Shada Wadi-Ramahi, W. Al-Najjar and B. Moftah "Failure Mode and Effects Analysis (FMEA) for improving Quality Assurance for Image-Guided High Dose Rate (HDR) Brachytherapy", Proceedings of IFMBE, Vol 51, World Congress on Medical Physics and Biomedical Engineering (WC 2015), Toronto, Canada July 7th -12th, 2015. ISBN: 978-3-319-19386-1 (Print) 978-3-319-19387-8 (Online).
- Shada Wadi-Ramahi, W. Al-Najjar and B. Moftah "Medical Physics Residency Program in Developing Countries: Lessons, Challenges and Solutions Learned from a Regional Pilot Training Program", Proceedings of IFMBE, Vol 51, World Congress on Medical Physics and Biomedical Engineering (WC 2015), Toronto, Canada July 7th -12th, 2015. ISBN: 978-3-319-19386-1 (Print) 978-3-319-19387-8 (Online).
- Shada Wadi-Ramahi, "Physics is a Waste of Your Intelligence", Proceedings of IFMBE, Vol 51, World Congress on Medical Physics and Biomedical Engineering (WC 2015), Toronto, Canada July 7th -12th, 2015. ISBN: 978-3-319-19386-1 (Print) 978-3-319-19387-8 (Online).

POSTERS AT CONFERENCES AND MEETINGS

- J. Khader, S. Alramahi, A. Almousa, F. Abu Hijleh, S. Alheet, I. Rashdan. "Requirements and Implementation of Lung SBRT Program in Developing Countries: Benefit of International Cooperation." 16th World Conference on Lung Cancer. 6-9 September 2015, Denver Colorado
- S. Aldelaijan, F. Alzorkany, B. Moftah, F. Alrumayan, J. Seuntjens, D. Lewis, S. Devic, "SU-E-T-665: Radiochromic Film Quenching Effect Reduction for Proton Beam Dosimetry," 57th AAPM, Anaheim, USA (2015).
- B. Moftah, Ahmad Basfar, Khalid Rabaeh, Akram Almousa, M Abdullah Al Kafi, Slobodan Devic, Radiation response of an improved optical CT based 3D gel dosimeter for radiation therapy quality assurance, Poster Discussion, ESTRO 3rd Forum, Barcelona, Spain, 24-28 April 2015.
- S. Aldelaijan, S. Devic, M. Shehadeh, F. Alzorkany, K. Al-Hadyan, G. Alsbeih, J. Seuntjens, B. Moftah, "PD-0444: Dose calibration and monitoring for radiobiological experiments with low energy proton beams," selected for the 'ESTRO Young Scientists Poster Session' scheduled within the Young Scientist Programme, 3rd ESTRO Forum, Barcelona, Spain (2015).
- L. Liang, H. Bekerat, N. Tomic, F. DeBlois, T. Vuong, S. Devic, A. Nobah, M. Mohiuddin, B. Moftah, Optimal Beam Quality for Linac-based Spatially Fractionated Grid Radiation Therapy (SFGRT), Poster abstract OF3-0098, 3rd ESTRO Forum, Barcelona, Spain, 24-28 April 2015.
- S. Devic, H. Mohammed, S. Aldelaijan, N. Tomic, J. Seuntjens, F. DeBlois, S. Lehnert, S. L. Faria, "PO-0773: FDG based glycolytic biological target volume: Warburg effect vs hypoxia," 3rd ESTRO Forum, Barcelona, Spain (2015).

RADIATION SAFETY OFFICE

HEAD

Fareed Mahyoub, MSc, MIPEM

MEMBERS

Ibrahim Al-Gain, MSc, MIPEM

Celestino Lagarde, BSc

THE MAIN OBJECTIVE OF THE RADIATION SAFETY OFFICE IS TO ensure the safe use of radiation throughout the hospital. The radiation safety program acts as the outline of our role in achieving our objective. There are mainly two aspects to our responsibilities; one related to the national regulatory body i.e. King Abdullah Center for Renewable and Nuclear Energy (KA-CARE) and the second one is related to the enforcement of national and international regulation within the vicinity of the hospital.

During 2015, the RSO successfully demonstrated to the national regulatory body, KA-CARE, our continuous eligibility to maintain our license to operate a radiotherapy facility and a Scientific Research Facility. The RSO has also submitted the necessary paper work to KA-CARE in order to prove our continuous eligibility to maintain our license to operate a Secondary Standard Dosimetry Laboratory, a health physics lab where leak test are performed and a personal dosimetry Lab.

With regards to the second part of our responsibility, the RSO performed many periodical tasks to ensure the safe usage of radioactive material within the hospital. Here is the list of tasks performed during 2015:

1. Performed a complete inspection of more than 350 radioactive sources that were imported for various end users within the hospital.
2. Surveyed and inspected more than 3,300 boxes containing radioactive materials produced by KFSH&RC Cyclotron Department before being shipped to the end users.
3. Safely disposed more than 350 used technicium-99 generators.
4. Over 675 leak test was performed
5. Investigated and followed up with around 10 staff whom occupational dose exceeded the ALARA level set by the hospital.
6. 35 Internal bioassays were performed to check the internal dose obtained by staff working with open sources.
7. The RSO performed intensive shielding verification for the new nuclear medicine and diagnostic facilities established at King Abdullah Center for Oncology and Liver Diseases.
8. More than 500 barrel containing decayed radioactive active waste were safely disposed through the Environmental Services at KFSH&RC.
9. The RSO played an important role in the inspection and the proper upgrade of radiation units at the Secondary Standard Dosimetry Laboratory Section at KFSH&RC.
10. The RSO played a vital role in training and educating more than 100 medical physics staff working for the Ministry in Radiation Protection.

SECONDARY STANDARD DOSIMETRY LABORATORY

HEAD
Mehenna Arib, PhD

MEMBERS
Omar Noor, MSc
Heba Al-Humidan, BSc
Huda Al-Ghamdi, BSc

THE SECONDARY STANDARD DOSIMETRY LABORATORY (SSDL) IN the Biomedical Physics Department of KFSH&RC-Riyadh has continued to provide high accuracy in radiation measurements and dosimetry for all applications of ionizing radiation. The high accuracy in measurement is maintained by successfully meeting the high standards set by the International Atomic Energy Agency (IAEA) and the World Health Organization (WHO) for radiation protection and radiotherapy levels of calibration. It gained the IAEA recognition as the first SSDL in the Kingdom to obtain the IAEA and WHO accreditation thus making it a recognized calibration laboratory in the whole world. It is also recognized by Saudi Arabia Nuclear Authorities as the only reference laboratory for instrument calibration in the Kingdom that meets national regulatory requirements and international standards. The SSDL continues to provide services to the different Departments of King Faisal Specialist Hospital and Research Centre (KFSH&RC) and to other institutions in the Kingdom of Saudi Arabia and the Gulf region.

By the end of 2014 new irradiation facilities were installed including a new 137Cs gamma irradiator, two X-ray machines for radiation protection and diagnostic calibrations and a 60Co unit for the calibration of radiotherapy instruments, mainly ionization chambers. These facilities were completely commissioned in 2015.

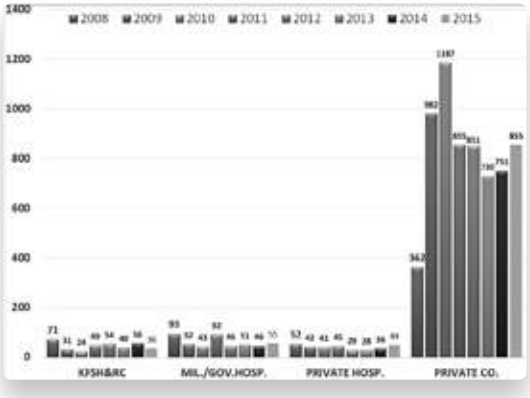


Figure 1. Number of instruments calibrated for external clients.

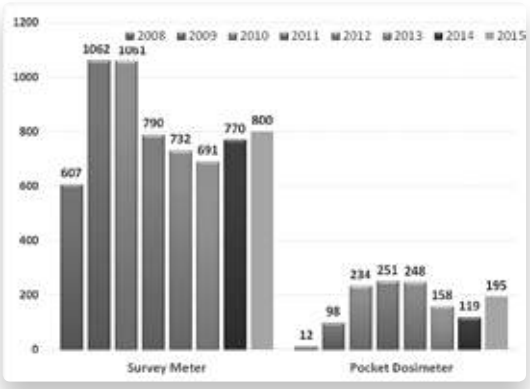


Figure 2. Type and number of instruments calibrated.

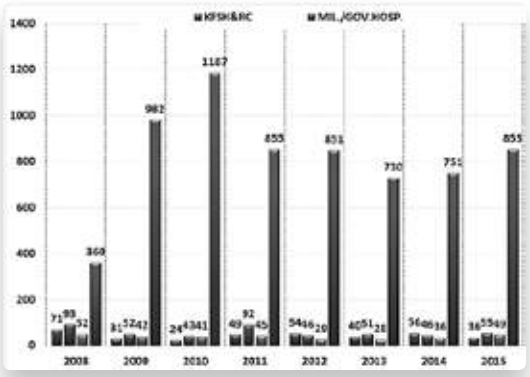


Figure 3. Number of instruments calibrated per year.

SUMMARY OF ACHIEVEMENTS IN 2015

ESTABLISHMENT OF THERAPY LEVEL CALIBRATION CAPABILITIES

1. Commissioning of the therapy level calibration unit
   - Verification of the safety system (interlocks, emergency switch off)
   - Radiation Safety survey around the Cobalt-60 unit
   - Verification of the beam alignment with the light field
   - Verification of the source position using inverse square law
   - Verification of the beam and light fields congruence
   - Determination of the beam profiles in reference conditions, in air and in water
   - Determination of the timer error
   - Calibration of the distance digital indicator
   - Verification of the Optical Distance Indicator
   - Verification of field size digital indicators (x and y)

2. Upgrading of the Cobalt-60 calibration unit
   - Installation of an Optical Distance Indicator
   - Installation of a digital field size indication system
   - Installation of a Central Beam Axis laser
   - Installation of a monitoring system (camera + monitor)

3. Establishment of calibration procedures of ionization chamber used in radiotherapy in terms of absorbed dose to water
   - Calibration of the reference chamber (NE 2561 # 291) and its electrometer (TN 10001 # 11631) at the dosimetry laboratory of the Internationals Atomic Energy Agency (IAEA)

- Design and fabrication of 1 mm thick waterproofing sleeves for the reference chambers
- Cross calibration of laboratory thermometers and barometers
- Determination of the reference absorbed dose to water in reference condition and study of its stability with time
- Calibration of the routine chamber (NE 2571# 1203) and its electrometer (NE 2570/1 # 1285) at the KFSH&RC SSDL
- Calibration of several ionization chambers and study of the variation of the calibration coefficient with time
- Calibration of plane parallel ionization chambers using an RW3 solid water phantom
- Development of a software (dose calculation, irradiation time, calibration of ionization chambers)
- Evaluation of uncertainty components and establishment of uncertainty budget for the calibration of ionization chambers
- Participation to the IAEA TLD dose audit for radiotherapy

ESTABLISHMENT OF RADIATION PROTECTION CALIBRATION CAPABILITIES

1. Commissioning of the Gamma irradiation units (multisource and New Cs-137 unit)
2. Commissioning of the 320 kV X-ray tube
3. Development of calibration procedures of for the calibration of survey meters in gamma and x-ray beams
   - Calibration of the reference chamber (FWT 1000 cc # 415-KGT) at the dosimetry laboratory of the Internationals Atomic Energy Agency (IAEA) for Cs-137, Co-60 and ISO 4037 x-ray Narrow beams
   - Establishment of ISO 4037 x-ray beam qualities
   - Measurement of air kerma rates at different distances for the gamma beams and for different currents for x-ray beams
   - Calculation of operational quantities (ambient and personal dose equivalent, exposure) using conversion factors published by IAEA
   - Development of software for routine calculations (dose quantities versus the sources and the distance, irradiation times for the two major sources, distance for a given dose rate value, calibration of survey meters and dosimeters and issuance of calibration certificates)
   - Establishment of uncertainty budget for the calibration of survey-meters in x-ray and gamma beams

ESTABLISHMENT OF DIAGNOSTIC RADIOLOGY CALIBRATION CAPABILITIES

1. Commissioning of the 160 kV x-ray tube
2. Calibration of two reference chambers (Exradin A3 # 144 and Exradin A2 # 122) at the dosimetry laboratory of the Internationals Atomic Energy Agency (IAEA) for RQR beam qualities
3. Establishment of the diagnostic RQR2 to RQR10 beam qualities (Determination of the additional filtrations and measurement of the HVLS). Comparison with the results obtained by several Laboratories
4. Measurement of air kerma rates for all the qualities for current from 5 mA to 30 mA

CARDIOVASCULAR RESEARCH PROGRAM

CARDIOVASCULAR RESEARCH PROGRAM

DIRECTOR

Coralie I. Poizat, PhD

MEMBERS

Abdullah Al Kulaib, *Administrative Assistant*
Salma Mahmoud, PhD, *Scientist*
Nadya Al-Yacoub, PhD, *Post Doctoral Fellow*
Vineesh Ravendran, PhD, *Associate Scientist*
Muhammad Kunhi, MSc, *Research Associate*
Qamar Al-Haffar, BSc *Research Assistant (Grant)*
Israa Ibrahim, Research Assistant *(Grant)*
Jawahir Nur, Research Assistant *(Grant)*
Lama Pharaon, BSc, *Masters Student*

PART-TIME MEMBERS

Qussay T. Marashli, *Medical Student (Al Faisal University)*
Karim Belhaj, *Medical Student (Al Faisal University)*
Yahya Reaf, *Medical Student (Al Faisal University)*
Sarah Al Shalan, *Undergraduate Student (Al Faisal University)*

THE CARDIOVASCULAR RESEARCH PROGRAM FOCUSES ON understanding molecular genetic and epigenetic mechanisms regulating cardiovascular diseases. The program has three major units investigating: 1) Epigenetic mechanisms regulating heart failure, 2) genetic mutations causing familial dilated cardiomyopathy and 3) the role of the Low Molecular Weight Protein Tyrosine Phosphatase in cardiovascular diseases. Our goal is to uncover fundamental new mechanisms controlling cardiac hypertrophy and heart failure, which remain the major cause of death in the Saudi population and worldwide. We use comprehensive methodologies in cellular systems, animal models and samples from patients in end-stage heart failure that underwent heart transplant to understand intracellular signaling pathways, transcriptional regulatory networks and epigenetic events in the normal and the diseased heart. The long-term goal is to use the new information generated in the laboratory to develop therapies to improve the health of patients with cardiovascular disorders

RAC APPROVED RESEARCH PROJECTS

PROJECT TITLE: Epigenetic Regulation by Nuclear CaMKII in the Heart

Role: Principal Investigator
Funding: KFSH&RC and KACST

AIMS: Calcium/calmodulin-dependent protein kinase II (CaMKII) enzymes play a central role in major cardiovascular disorders. Several isoforms expressed in various sub-cellular compartments regulate contractile activity and gene expression. A few years ago, we reported that nuclear CaMKIIδ acts as a novel epigenetic modifier to remodel chromatin in cardiac cells through histone H3 phosphorylation (Awad et al., *Nucleic Acid Res*. 2013). During this past year and with the help of our collaborators from the Heart Centre, the Pathology Department and the Comparative Medicine Department at KFSH&RC, we studied the *in vivo* role of CaMKIIδ as a histone-modifying enzyme and were able to show that CaMKIIδ directly couples calcium signals to chromatin under pathological stress. Using heart tissue explants from patients that underwent cardiac transplantation and CaMKIIδ-deficient mice subjected to pathological stress, we found that CaMKIIδ is recruited and H3 is hyper-phosphorylated at hypertrophic genes. This allows binding of the chaperone protein 14-3-3 to phosphorylated H3 resulting in elongation of fetal cardiac genes by RNA polymerase II. This study revealed a new paradigm of transcriptional control in the heart, implicating CaMKIIδ as a new epigenetic modifier and revealing a new point of control to design novel strategies to treat a variety of cardiac disorders (Awad et al. *J Pathol*, 2015).

Under this project, we continued to search for novel genetic mutations causing dilated cardiomyopathy (DCM) in human. DCM is a disease of the cardiac muscle characterized by a dilation of the left ventricle and thinning of the ventricular wall associated with reduced contractile function. In Saudi Arabia ~ 25% are inherited and referred to as familial DCM. In collaboration with the Heart Centre (Dr Jehad Al-Buraiki) and the Developmental Genetics unit (Dr Fowzan Al-Kuraya) at KFSH&RC, we continued to enroll families with DCM and worked actively at identifying novel mutations causing the disease. Using genotyping and next generation sequencing, we identified new variants in several families that we are now characterizing functionally to demonstrate that they are truly pathogenic. This project will lead to the identification of novel cardiomyopathy genes. It will help develop new genetic testing to diagnose DCM, which remains a significant burden in Saudi Arabia.

In collaboration with the group of Mark Sussman at San Diego State University (California, USA) we investigated the role of nuclear CaMKIIδ in cardiac progenitor cell (CPC) lineage commitment. CPC arise from the differentiation of embryonic stem cells and are found in the adult heart. Yet, the role of calcium signals in CPC biology was unknown. In this study, we investigated whether CaMKIIδ is present in resident CPCs and its role in CPC differentiation. Our study demonstrated nuclear translocation of CaMKIIδ upon CPC commitment. Forced expression of CaMKIIδ facilitates CPCs survival and differentiation into cardiomyogenic lineages. These results suggest that nuclear CaMKIIδ may be used as a mean to enhance CPCs therapeutic potential for heart regeneration (Quijada et al., J. Biol. Chem., 2015).

PROJECT TITLE: CaMKII Epigenetic Signaling in Heart Diseases

Role: Principal Investigator
Funding: KFSH&RC and KACST

AIMS: The goal of this research project is to establish a new epigenetic mechanism regulating heart

failure, which remains a major cause of death in the Kingdom of Saudi Arabia and worldwide. We have recently discovered that CaMKII enzyme signals to chromatin by altering H3 phosphorylation, which changes chromatin structure to activate transcriptional events leading to pathological cardiac hypertrophy. The goal of this project is to show that CaMKII enzyme also regulates H3 methylation. For this, we are using CaMKIIδ knockout mice to test that their resistance to pathological stress, is due to changes in histone phosphorylation and methylation status that alter chromatin structure and gene transcription. To understand how CaMKII-mediated signaling to histones regulates the development of heart failure, we are also performing sequencing of chromatin immunoprecipitates (ChIP-seq) to assess H3 phosphorylation and methylation landscapes in the normal heart and the diseased murine and human myocardium. This study will reveal which genes are regulated by CaMKII through phosphorylation and methylation genome-wide. We hope to use this new information on CaMKII biology to develop future new therapies based on epigenetic mechanisms for the treatment of cardiovascular disorders.

PROJECT TITLE: Role of LMPTP in Cardiovascular Diseases
Role: Principal Investigator
Funding: KFSH&RC and KACST

AIMS: Congestive heart failure remains a major cause of morbidity and mortality worldwide. Heart failure results from a number of common conditions including long-standing hypertension, myocardial infarction, coronary artery diseases, valve disease and various forms of cardiomyopathy. There is a strong need for therapies that can alleviate or reverse the loss of contractile function of a failing heart. With the help of the Comparative Medicine Department at KFSH&RC (Dr A. Assiri), we addressed the *in vivo* function of a protein phosphatase named LMPTP, encoded by the *ACP1* locus. Detailed functional and biochemical studies performed in *ACP1* knockout mice revealed that deletion of *ACP1* confers a striking protective phenotype. *ACP1* knockout mice are resistant to long-term pressure overload hypertrophy, have reduced fibrosis and reduced expression of heart failure markers compared to wild-type mice. Transcriptional analysis and analysis of molecular signaling showed that the resistance of *ACP1*-deficient mice to pathological stress is due to activation of several protective pathways such as the insulin receptor beta and inhibition of deleterious pathways such as CaMKII signaling. This study suggests that inhibition of the protein phosphatase may offer a new therapeutic approach for the treatment of heart failure in human (Wade et al., *J Pathol*, 2015).

We also investigated the role of *ACP1* polymorphism in cardiovascular disorders in the Saudi population. For this, we performed a large-scale association study in Saudi patients with coronary artery diseases, in collaboration with the Cardiovascular & Pharmacogenomics unit of the Genetics Department at KFSH&RC (Dr Nduna Dzimiri). The association study performed in about 2,500 patients with coronary artery disease and the same number of normal individuals revealed several variants that confer risk for low-level HDL and obesity. One variant located in the promoter region of the *ACP1* gene was associated with protection against coronary artery disease. The significance of this study is to establish the role of a novel phosphatase in dyslipidemia and obesity. This study should help develop new tools for the diagnosis of metabolic disorders in the Saudi population.

PROJECT TITLE: Project 4 and Project 5
Role: Co-Investigator
Funding: KFSH&RC

PRINCIPAL INVESTIGATORS: *F. Al Kuraya & N Al Tassan*

AIMS: We performed functional work and provided support for two studies for the group of Dr Fowzan Al-Kuraya (Developmental Genetics unit, Genetics Department, KFSH&RC) and the group of Dr Nada Al-Tassan (*Behavioral Genetics*). The first study identified a mutation in TLE6 that causes the earliest known human embryonic lethality (Al-Azami et al., *Genome Biol.*, 2015). The second collaboration resulted in the identification of a novel mutation in COL25A1 causing congenital cranial dysinnervation disorder (Shinwari et al., *Am J Hum Genet*, 2015).

SELECTED ACHIEVEMENTS FOR 2015

- Completed several studies resulting in oral presentations at local and international conferences and peer-reviewed manuscripts published in a high-impact factor journals.
- Established a new method of myocardial infarction in mice to create a mouse model of heart failure with lower mortality rate.
- Maintained local collaborations with the Heart Centre, the Cardiovascular & Pharmacogenomics unit, the Developmental Genetics unit, the Pathology Department, the Department of Biostatistics, Epidemiology & Scientific Computing, and the Comparative Medicine Department at KFSH&RC.
- Maintained international collaborations with the Heart Institute (Mark Sussman) at San Diego State University, San Diego, USA and with the La Jolla Institute for Allergy & Immunology (Nunzio Bottini), La Jolla, San Diego, and with the laboratory of Donald Bers, University of California at Davis, California, USA.
- Trained medical students from Al-Faisal University, local high school students and undergraduate students.

PRESENTATION AT LOCAL AND INTERNATIONAL CONFERENCES (LAST 3 YEARS)

LOCAL

- Hakoun A, Al-Yacoub N, Al-Habeeb W and Poizat C. Identification of New Genetic Loci in Familial Dilated Cardiomyopathy. 4th Annual Research Day, Al Faisal University College of Medicine, 10 April 2013.
- Marashly Q, Mahmoud S and Poizat C. Role of CaMKII as a chromatin Remodeler in Cardiac Hypertrophy. 4th Annual Research Day, Al Faisal University College of Medicine, 10 April 2013.
- Invited Speaker at the College of Medicine-Biomedical Research Seminar Series. Al Faisal University, Riyadh, Saudi Arabia. Nuclear Calcium Signaling to Chromatin in the Heart. January 13, 2013.
- Invited Speaker, Cardiac Sciences Ground Round, King Fahad Cardiac Centre, College of Medicine, King Saud University, Jan 7, 2014.
- Keynote Speaker – 2013 Annual Research Day, "Epigenetic Reprogramming by Histone Modifications in Cardiac Diseases", King Faisal Specialist Hospital & Research Centre, 16-17 April 2014.
- Invited Speaker, Saudi Heart Failure Conference. Genetic ablation of *ACP1* prevents cardiac dysfunction and attenuates fibrosis after pressure overload, Jeddah, Saudi Arabia, 4-5 Dec 2015.

INTERNATIONAL

- Awad Mahmoud S, Kunhi M, Little GH, Bai Y, An W, Bers D, Kedes L, Poizat C. Nuclear

CaMKII is a Histone H3 Kinase that Remodels Chromatin During Cardiac Hypertrophy. Basic Cardiovascular Sciences conference, July 22–25, 2013, Las Vegas, Nevada, USA.

- Invited Speaker at the Saudi International Conference for Medical Technology. Epigenetic Reprogramming by Calcium-dependent Protein Kinase II in Heart Failure. September 20–30, 2013.
- SM Awad, MS Al-Dosari, N AlYacoub, D Colak, MA Salih, FS Alkuraya and C Poizat. 5th Annual World DNA and Genome Day 2014. A Novel Mutation in PHC1 Links Chromatin Remodeling to Primary Microcephaly Pathogenesis. Dalian, China, April 25–28, 2014.
- Invited Speaker, Heart Failure Association Conference, Les Diablerets, Switzerland. "Epigenetic Aspects in Heart Failure, Histone Phosphorylation" January 22–25, 2014.
- Invited Speaker, International Society for Heart Research "CaMKII epigenetic control of histone H3 phosphorylation in heart failure" Miami, Florida, USA, 11–15 May 2014.

POSTER PRESENTATIONS BY POST-DOCTORAL FELLOWS, MEDICAL STUDENTS, UNDERGRADUATE & GRADUATE STUDENTS

- Awad Mahmoud S, Aldosari M., Al Yacoub N, Sogaty S, Salih MA, Alkuraya F, Poizat C. Mutation in *PHC1* Implicates Chromatin Remodeling in Primary Microcephaly Pathogenesis. Cold Spring Harbor Laboratory Conference "Epigenetics & Chromatin", September 11–15 2012.
- AS Al-Oneazi, NM Al-Rasheed, HA Attia, NM Al-Rasheed, RA Mohamad, MA Al-Amin, C Poizat. Investigation of the Inhibitory Effect of Ruboxistaurin on the Activity of Smad and GRAP Proteins in Diabetic Induced Nephropathy Rat Model. Diabetes UK Professional Conference. 13–15 March 2013.
- Awad Mahmoud S, Kunhi M, Little GH, Bai Y, An w, Bers D, Kedes L, Poizat C. Nuclear is a Histone Histone H3 Kinase that Remodels Chromatin During Cardiac Hypertrophy. Basic Cardiovascular Sciences conference. July 22–25, 2013 Las Vegas, Nevada, USA.
- AlShalan S, Mahmoud S and Poizat C. Expression Profiling of Epigenetic and Chromatin Remodelers Factors in Human Heart Failure. 5th Annual Research Day, Al Faisal University College of Medicine, 10 April 2014. 2nd place winner.
- Belhaj K, Wade F and Poizat C. Identification of Putative Substrates of A Protein Phosphatase in the Heart. 5th Annual Research Day, Al Faisal University College of Medicine, 10 April 2014.
- QuijadaP, Hariharan N, CubilloJ, Bala K.M, OrmacheaL, Bers D, Sussman M and Poizat C. Nuclear Calcium/Calmodulin-Dependent Protein Kinase II Signaling Enhances Cardiac Progenitor Cell Survival and Cardiac Lineage Commitment. AHA Basic Cardiovascular Science conference, New Orleans, Louisiana, July 13–16, 2015.
- Awad S.M., Wade F, Quijada P, Al-Haffar KM, Kunhi M, Toko H, Marashly Q, Belhaj K, Ibrahim E, Stanford SM, Alvarez R, Liu Y, Colak D, Jordan MC, Roos KP, Al-Habeeb W, Sussman M, Bottini N and Poizat C. Deletion of Low Molecular Weight Protein Tyrosine Phosphatase (*ACP1*) Protects Against Stress-Induced Cardiomyopathy. Orlando, Florida, November 7–11, 2015.

PEER-REVIEWED PUBLICATIONS

- Awad Mahmoud S, Aldosari M., Al Yacoub N., Sogaty S, Salih MA, Al Kuraya F., Poizat C. Mutations in PHC1 Implicates Chromatin Remodeling in Primary Microcephaly Pathogenesis. *Hum Mol Genet*. 2013 Jun 1;22(11):2200-13.
- Awad Mahmoud S, Kunhi M, Little GH, Bai Y, An w, Bers D, Kedes L, Poizat C. Nuclear CaMKII Enhances Histone H3 Phosphorylation and Remodels Chromatin During Cardiac Hypertrophy. *Nucleic Acids Res*. 2013 Sep;41(16):7656-72.
- Awad Mahmoud S and Poizat C. Epigenetics & Chromatin Remodeling in Adult Cardiomyopathy. Journal of Pathology, 2013 Oct;231(2):147-57.
- Shaheen R, Shamseldin HE, Loucks CM, Seidahmed MZ, Ansari S, Ibrahim Khalil M, Al-Yacoub N, Davis EE, Mola NA, Szymanska K, Herridge W, Chudley AE, Chodirker BN, Schwartzentruber J, Majewski J, Katsanis N, Poizat C, Johnson CA, Parboosingh J, Boycott KM, Innes AM, Alkuraya FS. Mutations in CSPP1, Encoding A Core Centrosomal Protein, Cause A Range of Ciliopathy Phenotypes in Humans. *Am J Hum Genet*. 2014 Jan 2;94(1):73-9.
- Shareef MA, Anwer LA and Poizat C. Cardiac SERCA2A/B: Therapeutic Target for Heart Failure. *European Journal of Pharmacology*. 2014 Feb 5;724:1-8.
- Awad S, Al-Haffar KM, Marashly Q, Quijada P, Kunhi M, Al-Yacoub N, Wade FS, Mohammed SF, Al-Dayel F, Sutherland G, Assiri A, Sussman M, Bers D, Al-Habeeb W, Poizat C. Control of Histone H3 Phosphorylation by CaMKIIδ in Response to Haemodynamic Cardiac Stress. *J Pathol*. 2015 Mar;235(4):606-18.
- Shinwari J, Khan A, Awad SM, Shinwari Z, Alalya A, Alanazi M, Tahir A, Poizat C, Al Tassan N. Recessive Mutations in COL25A1 are a Cause of Congenital Cranial Dysinnervation Disorder. Am J Hum Genet. 2015 Jan 8;96(1):147-52.
- Wade FS, Quijada P, Al-Haffar K, Awad SM, Kunhi M, Toko H, Marashly Q, Belhaj K, Stanford SM, Alvarez R, Liu Y, Dilek Colak, Jordan MC, Roos KP, Al-Habeeb W, Sussman MA, Bottini N and Poizat C. Deletion of Low Molecular Weight Protein Tyrosine Phosphatase (Acp1) Protects Against Stress-Induced Cardiomyopathy. *J Pathol*. 2015 Jul 25.
- QuijadaP, Hariharan N, CubilloJ, Bala K.M, Emathinger JM, Wang BJ, OrmacheaL, Bers D, Sussman M and Poizat C. Nuclear Calcium/ Calmodulin-Dependent Protein Kinase II Signaling Enhances Cardiac Progenitor Cell Survival and Cardiac Lineage Commitment. *J Biol Chem*. 2015 Oct 16;290(42):25411-26.
- Alazami AM, Mahmoud SA, Coskun S, Al-Hassan S, Hijazi H, Abdulwahab F, Poizat C*, Alkruaya FS*. TLE6 Mutation Causes the Earliest Known Human Embryonic Lethality. *Genome Biol*. 2015 Nov 5;16(1):240. * co-corresponding authors.

CELL BIOLOGY

CELL BIOLOGY

CHAIRMAN

Futwan A Al-Mohanna, PhD, FRSB, FRSC

ADMINISTRATIVE SUPPORT STAFF

Camelia Touzinte

Rita Sison

THE DEPARTMENT OF CELL BIOLOGY IS COMPLETING ITS 4TH YEAR of existence contributing to both medical and biological sciences with attention to and emphasis on the field of cardiovascular biology/xenotransplantation, diabetes research, aerobiology, cellular imaging/molecular signaling and training of many Saudi nationals. The Department was established to focus on the temporal and spatial relationships between extra-cellular stimuli and intracellular second messenger generation. Stimulus-response coupling is studied in a variety of conditions, namely, innate immune responses, xeno-and-allogeneic interactions, nucleo-cytoplasmic signaling and aberrant signaling in diseases like metabolic syndrome and diabetic retinopathies.

The Department has four main sections: Cardiovascular Biology Section, the Diabetes Research Unit, Allergy and Medical Aerobiology Section and the Cell Imaging and Molecular Signaling. The research activities are described in the subsequent sections that follow.

XENOTRANSPLANTATION RESEARCH

HEAD
Futwan A Al-Mohanna, PhD, FRSB, FRSC

MEMBERS
Ranjit Parhar, PhD
Mohammed Quttainah, MD
Reem Al-Hejailan
Rana Al-Rabiah
Soad Saleh
Razan Bakheet
Azizah Al-Anazi
Hussein Al-Hindas
Mashael Al-Saud
Ghassan Dardas
Somaya Al Qattan
Nujud Al Saiari

THIS SECTION IS DEVOTED TO FINDING VIABLE SOLUTIONS TO THE need for health interventions in Cardiovascular patients who are no longer responding to pharmaceutical and/or surgical intervention. Currently there are very limited alternatives to heart transplantation, and the number of patients with this disease is increasing annually.

Due to the profound lack of donor organs for transplantation, many patients with end-stage heart failure succumb to fatalities during the wait for a suitable organ replacement. Xenotransplantation provides a viable alternative for such replacement. However, many immunological and physiological barriers are still to be negotiated before xenotransplantation becomes a clinical reality. Moreover, even with genetic modification of donor organs to overcome the hyperacute rejection and immune suppression to dampen the rejection process, vascularized xenografts remain unable to provide the lasting acceptable cardiac function in the recipient. Studying the molecular and cellular mechanisms of xenograft rejection is the main focus of this section.

SECTION'S ACTIVITIES

The Xenotransplantation Unit has been active in researching the mechanisms which prevent successful xenotransplantation. The results of our endeavors have identified innate immune cells, namely the human naive neutrophils and NK cells of the recipient, as major players in recognizing xenoantigens independently of humoral responses associated with xenoreactive natural antibodies and complement that normally leads to hyperacute rejection of transplanted vascularized xenograft.

RAC AND KASCT APPROVED PROJECTS

PROJECT TITLE: The use of Rat Embryonic stem cells in Decellularized Rat Heart
RAC# 2110-011

INVESTIGATORS: *Dr. Futwan Al-Mohanna (PI), Kate Collison (Co PI), Ranjit Parhar, Reem Al-Hejailan, Falah Al-Mohanna, Abdullah Assiri, Zouhair Halees, Mail Al-Shahad, Mohanna Al-Mohanna and Sultan Al- Sedairy*

PROGRESS: In progress.

PROJECT TITLE: Role of KLF3 in Fatty Acid B-Oxidation: Towards Combating Obesity
RAC # 2130-6: Bio 2074-20

INVESTIGATORS: *Ranjit Parhar (PI), Futwan Al-Mohanna (Co PI), Kate Collison, Sarwar Hashmi*

PROGRESS: In progress.

PROJECT TITLE: IL-12 Gene Therapy of Thyroid Cancer in BRAF^{V600E} Transgenic Mouse Model
RAC# 2130-7: BIO 1434-20

INVESTIGATORS: *Yufei Shi (PI) Minjing Zou (Co PI), Ranjit Parhar*

PROGRESS: In progress.

PROJECT TITLE: Characterization of Lacrimal and Ocular Mucosal Immunity in the Arabian Camel (*Camelus dromedaries*)
RAC#2130-8: BIO 2073-20

INVESTIGATORS: *Walter Conca (PI), Futwan Al-Mohanna (Co PI), Ranjit Parhar*

PROGRESS: In progress.

PROJECT TITLE: Phenotypic and Gene Expression Profiling and their Correlation with Clinical Outcomes During the Development and Progression of Diabetic Retinopathy in Type 1 Diabetes Mellitus
KASCT Project # 10-BIO956-20

INVESTIGATORS: *M De Niro (PI) & F Al-Mohanna*

PROGRESS: In progress.

DIABETES RESEARCH

HEAD

Kate S. Collison, PhD, FRSB, FRSC

MEMBERS

Angela Inglis
Bernard Andres
Rosario Ubungen
Jennifer Thiam
Sherin M Shibin
Princess Mata

THE GLOBAL PREVALENCE OF DIABETES IS ESTIMATED TO BE ABOUT 9% of the world population. Our research program examines the contribution of specific micro-and macronutrients to the development of glucose deregulation and obesity. Diabetes is a risk factor for other metabolic diseases, such as Non-Alcoholic Fatty Liver Disease (NAFLD); and patients with diabetes are more likely to suffer from age-related cognitive impairment. We have identified several additions to the global diet in recent decades which have contributed to the growing epidemic of obesity & diabetes (diabesity). It is becoming clear that consumption of dietary sugars is most likely the major culprit in promoting obesity. We were one of the first laboratories to demonstrate the mechanism whereby dietary High Fructose Corn Syrup (HFCS) contributes to diabesity by disrupting liver function, promoting increased fatty deposition, the generation of reactive oxygen metabolites, and mitochondrial disruption. We have also shown how HFCS alters hepatic and adipose tissue gene expression, which can be further modulated by the ubiquitous food additive Monosodium Glutamate (MSG).

Recent epidemiological data in humans suggests that consumption of zero- or low-calorie sweeteners is associated with a paradoxical increase in weight gain. Aspartame consumption has also been linked with neurological complaints in humans. However, correlation does not imply causation. Our research shows that lifetime exposure to the artificial sweetener Aspartame (a widely consumed low-calorie sweetener), commencing neonatally, may disrupt glucose homeostasis leading to weight gain in adulthood. Our behavioral studies showed that neonatal aspartame exposure may deleteriously affect certain aspects of behavior such as spatial learning and memory. We also found that the commonly consumed food additive Monosodium Glutamate (MSG) can interact with Aspartame to further impair glucose homeostasis, but the mechanism for this remained unknown. We recently hypothesized that the effects of Aspartame on glucose homeostasis may occur in part at the level of N-Methyl D-Aspartate (NMDA) Receptor interactions. NMDARs are located in the brain hypothalamus, an area which controls glucose homeostasis, energy balance, and certain aspects of learning and memory. We have employed a competitive selective NMDA receptor antagonist, CGP39551 which is an experimental anticonvulsant drug, to ascertain to what extent the effects of neonatal exposure to Aspartame and / or MSG are mediated by NMDA receptor interactions.

RAC AND KACST-APPROVED PROJECTS FOR THE DIABETES RESEARCH SECTION

PROJECT TITLE: Interactive Effects of Neonatal Exposure to Excitatory Amino Acids on Normal Metabolism, Learning and Memory: Role of N-Methyl D-Aspartate Receptors
RAC 2130 011

INVESTIGATORS: *Kate Collison (PI), Futwan Al-Mohanna, Angela Inglis, Bernard Andres*

PROGRESS: In progress.

PROJECT TITLE: Potential Role of Glutamate as an Immunoregulator: Effect on Neutrophil function
RAC# 2130 038

INVESTIGATORS: *Kate Collison (PI), Futwan Al-Mohanna, Angela Inglis, Bernard Andres*

PROGRESS: In progress.

PROJECT TITLE: Effects of N-Methyl D-Aspartate Receptor Antagonism on Food Additive-induced Neuroendocrine Impairment: A Double-edged Sword?
KACST #13-MED2506-20

PRINCIPAL INVESTIGATOR: *Kate Collison*

PROGRESS: In progress.

PROJECT TITLE: Clustering of Metabolic Syndrome in Spousal Pairs: A Simulation Modelling Strategy
RAC#2120 013

INVESTIGATORS: *Mohammed Shoukri (PI), Kate Collison*

THE DIABETIC RETINOPATHY PROGRAM

HEAD

Michael DeNiro, DVM, MVM, MSc

MEMBERS

Sally AlAhmar, MD *(Research Assistant)*

Areej AlQahtani, BSc *(Research Technical Assistant)*

THE PROGRAM INVESTIGATES HYPOXIA/HYPEROXIA-INDUCED retinopathies in vitro and in vivo as a model for diabetes retinopathy. The work has led to the discovery of a small molecule inhibitor of HIF-1 alpha that can reverse the effect of hypoxic/hyperoxic insult on the retina. A Biotechnology grant has already been awarded for the continuation of this work.

Diabetic retinopathy is the most common diabetic eye disease and a leading cause of blindness. It is caused by changes in the blood vessels of the retina. By using diabetic animal models (type 1 and type 2 diabetes mellitus) of human retinal disease; Dr. DeNiro and his team investigate prognostic (clinical and molecular) markers that are highly associated with diabetic retinopathy. These markers are investigated by using various approaches that assess functional, structural, cellular, and molecular changes. The Retinopathy Research Unit's scientific approach that combines data from electrophysiological, imaging, immunohistochemical, and molecular techniques to build a complete understanding of the pathophysiology of neuronal and vascular changes with diabetic retinopathy. These assessments provide a complete picture of the disease process and can be followed to develop an understanding of disease development and progression. The main thrust of Dr. DeNiro and his team's research has focused on; 1) understand the changes in neuronal and glial cell function that often occur prior to overt vascular abnormalities, 2) appreciate the link between glial cell dysfunction and changes in vasculature, 3) conduct target-based drug discovery studies to develop neuroprotective treatments for retinal diseases that could slow the progression of vision loss

PROJECT TITLE: Phenotypic and Gene Expression Profiling and their Correlation with Clinical Outcomes During the Development and Progression of Diabetic Retinopathy in Type 1 Diabetes Mellitus

RAC No. 2100016

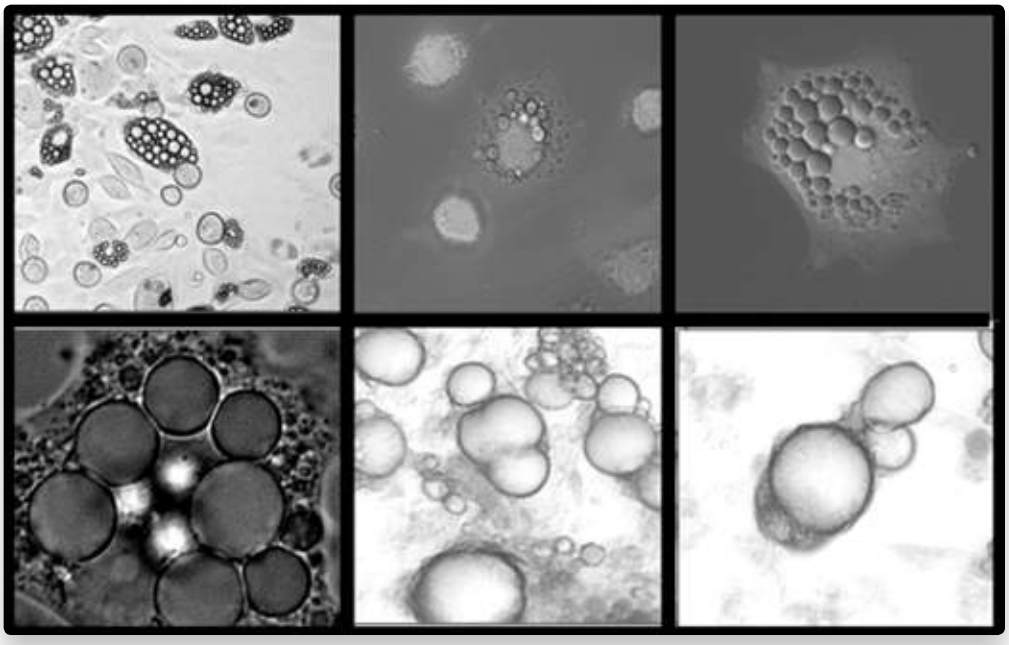
Source of Funding: King Abdulaziz City for Science and Technology (KACST).

PROJECT DESCRIPTION: The main objective of this study is to investigate and determine:

1. The phenotypic and gene expression changes that occur throughout the development and progression of diabetic retinopathy in the Akita (Ins2Akita) mouse model of type 1 diabetes mellitus, as compared to the C57/BL6J mouse
2. The correlation between the gene expression profile and the clinical course of diabetic retinopathy in the Akita (Ins2Akita) mouse model.

PROJECT TITLE: Role of KLF3 in Fatty Acid β-Oxidation: Towards Combating Obesity

PROJECT DESCRIPTION: This collaborative work focuses on extending the finding that mutation in the Krüpple like transcription factor (KLF3) in C elegans which cause fat accumulation may also occur in mammals through similar mechanism(s).



ALLERGY AND AEROBIOLOGY

HEAD

Syed M. Hasnain, PhD, FACAAI, FAAAAI

MEMBERS

Halima Al-Sini

Alanoud Al-Qassim

Abdulrahman Al-Sobhi

Mubarak Al-Enizi

Cheryl Mijares *(Allergotek/SDL)*

PROJECTS IN PROGRESS

PROJECT TITLE: Respiratory Allergic Diseases in Saudi Arabia: A Program to Study Environmental Biological Pollutants and Toxic Fungi with the Establishment of a Biotechnology Laboratory for Continuation of the Program

NSTIP Project: Code 13-BIO814-20. (ongoing since May 2014)

INVESTIGATORS: *Dr. SM Hasnain (Co-I), Dr. Sultan Al-Sedairy (P.I)*

This project deals with the analysis of indoor allergenic protein, toxic fungi and endotoxins present in the patient's indoor environment. There appear to be no laboratory in the Middle East which is equipped with the state-of-the-art technology to detect and analyze allergenic microbes, their bi-products and/or their proteins fractions responsible for sensitization and elicitation of asthma and related respiratory allergy.

With the completion of Project, a community oriented services program will emerge using the equipment and facility. Currently we have MARIA (Multiplex Array for Indoor Allergens) and ELISA set to detect Der p 1, Der f 1, Bla g 1, Bla g 2, Per a 1, Fel d 1. House dust samples from both patients and control homes from several regions were included in our analysis in order to have a national representation.

The ultimate goal of this project is to provide services to patients, institutions, hospitals, schools and individuals. The publication of findings will create awareness and thereby expected to prevent and minimize the rising number of asthma and allergy cases in Saudi Arabia. As an estimate, the asthma care cost in the next 20-30 years in Saudi Arabia will exceed the total combined cost of cancer and cardiovascular diseases.

PROJECT COMPLETED IN 2015

PROJECT TITLE: Allergotek Diagnostic and Therapeutic Program

NSTIP Project (Bioincubator_3)

INVESTIGATORS: *Dr. SM Hasnain (Co-I), Dr. Sultan Al-Sedairy (P.I).*

The main objective of the project was to develop indigenous diagnostic and therapeutic products exclusively related and relevant to diagnosis and treatment of allergic diseases namely: bronchial asthma and allergic rhinitis. The selections of indigenous allergenic species in this project were based on many years of allergological research (and subsequent clinical and efficacy trial of the species in different regions of Saudi Arabia).

The project successfully concluded with the establishment of bench to bedside products and company called "Allergotek Ltd." The Company will continue research and development on the role of various indigenous allergens in the region along with production of Skin Prick Test and Immunotherapy vaccines for asthma and allergy patients.

PROJECT TITLE: Characteristics and Composition of the Falling Dust and Particulate Matter and its Health Hazards in Riyadh City, Saudi Arabia

King Saud University Project

INVESTIGATORS: *Dr. SM. Hasnain (Co-I), Prof. A.S Al-Modaihsh (P.I - KSU)*

A collaborative project with King Saud University, (Project Number 08ENV319-02). Concluded with sampling and analysis of allergenic pollen, fungal spores and falling dust particles in the environment of Riyadh.

The project completed with comprehensive data on airborne bacteria, fungi, pollen etc. Several manuscripts are under preparation.

PROJECT TITLE: Proteomics Analysis for *Amaranthus* *(KACST ARP-27-11 (RAC project #2050 029)*

In collaboration with Proteomics Unit of Stem Cell & Tissue Engineering Department (Dr. Ayodele Alaiya), we continued analyzing the data collected. The study revealed some Allergy stimulating molecules in Allergy patients challenged with *Amaranthus* extracts. The proteomics definition of protein biomarkers may become potential tool for Allergy and Asthma diagnosis. One paper has been published and one has been accepted.

PROGRESS: Project completed, data were analyzed and 3 manuscripts are ready for submission.

PROJECT SUBMITTED IN 2015

PROJECT TITLE: Environmental, Biochemical and Clinical Studies of *Conocarpus* Trees Pollen in the Kingdom of Saudi Arabia

INVESTIGATORS: *Dr. SM. Hasnain (Co-I), Prof. AR Al-Frayh (P.I - KSU)*

The *Conocarpus* trees (*Conocarpus lancifolus Engl.* & Diels Family Combretaceae) on the street of Riyadh and other parts of Saudi Arabia have been planted as ornamentals. The tree is known as Darzymia or *Damas* in Arabic. The English common name of the tree is buttonwood or button mangrove and has its origin in Africa, Middle East, and India. During the last 10 years, the numbers of *Conocarpus* trees have increased in the Kingdom of Saudi Arabia and anecdotal evidences are pouring that people living in the nearby or passing through the street, particularly in the morning, suffer from various respiratory illness including bronchial asthma, allergic rhinitis and conjunctivitis. Some people considered this plant and the smell of the plant to cause 0further diseases such as cancer. In order to have a biological and clinical evidence, scientific investigation and clinical studies are required so that we would be able to conclude the harmful aspect of *Conocarpus* pollens. This project was initiated in collaboration with Ministry of Agriculture, Riyadh Municipality and King Saud University (Submitted to KACST for approval).

CELL IMAGING AND MOLECULAR SIGNALING

THIS IS AN INTEGRATED TECHNOLOGY BASED APPROACH TO molecular signaling and cellular imaging. We provide technical expertise in cell biology to many researchers within and without the Research Centre. A number of imaging technologies are available in this facility, including ion-imaging microscopy and real-time live cell confocal imaging.

Quantitative intra cellular ion analysis and imaging is performed using the Axio vision, CLSM and Cell sense (image analysis software).

STATISTICAL AND BIOINFORMATICS:

By: Dr. Mohamed Shoukri, Principal Scientist

ORA APPROVED PROJECTS

- Diagnostic value of cardiac computed tomography angiography in patients with left bundle branch block and abnormal single photon emission computed tomography (*P.I. Dr. Bandar Al-Ghamdi*)
- The predictive value of heart rate variability in critical illness (*P.I. Dr. Nawal Salahuddin*).
- Validation of an Arabic questionnaire for symptom assessment (*P.I. Dr. Mohamed Al-Shahri*)
- Global analyses of gene expression across cancer types reveal a common mitosis/ chromosomal segregation AU-rich mRNA cluster regulated by key RNA-binding proteins (*Professor Abu-Khabar*).
- Access flow based intervention for management of arteriovenous hemodialysis access dysfunction (FBI): A prospective randomized controlled study (*P.I. Dr. Naveed Ul-Haq*).
- Carbapenem versus beta-lactam/ beta-lactamase inhibitor combination therapy for blood stream infectious caused by extended spectrum beta-lactamase (ESBL)-producing Enterobacteriacease; retrospective cohort study (*PI: Ali Omrani*).
- Risk factors for the outcomes of infections caused by carbapenem and colistin- resistant Gram-negative bacteria; a matched case-control study (*PI: Ali Omrani*).
- Molecular characterization, epidemiology, risk factors and outcomes of carbapenem-resistant Gram-negative infections.

KACST: APPLIED FOR

- Biological Monitoring of benzene and other pollutant exposure and its health impact among Saudi school living in Riyadh city. (*PI: Dr. Iman Al-Saleh*)

DEPARTMENT PUBLICATIONS

- Quttainah M, Al-Hejailan R, Saleh S, Parhar R, Conca W, Bulwer B, Moorjani N, Catarino P, Elsayed R, Shoukri M, AlJufan M, AlShahid M, Ouban A, Al-Halees Z, Westaby S, Collison K, Al-Mohanna FA. Progression of matrixin and cardiokine expression patterns in an ovine model of heart failure and recovery. *Int J Cardiol*. 2015;186:77-89. doi: 10.1016/j.ijcard.2015.03.156.
- DeNiro M, Al-Mohanna FA. Nuclear factor kappa-B signaling is integral to ocular neovascularization in ischemia-independent microenvironment. *PLoS One* 2014 Jul 22;9(7):e101602. doi: 10.1371/journal.pone.0101602.
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CENTER FOR AUTISM RESEARCH

CENTER FOR AUTISM RESEARCH

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THE CENTER FOR AUTISM RESEARCH (CFAR) CONTINUES TO FULFIL ITS mission to become and remain a center of excellence in the diagnosis, intervention, training and research of Autism Spectrum Disorder (ASD). Since January 2015, the multi-disciplinary team has conducted over 70 two-week diagnosis procedures, consulted with families with children with autism spectrum disorder and related disorders, and enrolled approximately 69 children in early intervention, therapeutic, and/or research studies.

One of the three most important activities that were undertaken during the year was our autism awareness campaign through workshops, lectures and trainings". Its purpose was to spread awareness and knowledge related to ASD and teaches parents their importance in the intervention process. The second important achievement was the expanding ASD research projects, this year we have achieved three new approved research projects such as: Factors Associated with the Use of Autism Services in Saudi Arabia, Public Awareness Toward Autism & It's Common Believes in Saudi Arabia and Oral Medicine Health Care and Challenges Facing Dentists and ASD Families at Dental Clinics in KSA and the third most important achievement was to established the capacity to deliver early intervention by certified practitioners and trainers and CFAR is proud to announce that we have increased the numbers of our certified specialists for early intervention and diagnosis such as: Early Start Denver Model (6 are now certified), ADI-R (5 specialists are certified), PECS (9 specialists are certified) and ADOS- 2 (1 employee is certified) through this the CFAR has been accepting trainees from different universities as well as rotating interns to be trained in the center. Currently we have trained 6 translators from Princess Noura University and 4 rotating residents from Pediatric Department, KFSH&RC.

RAC APPROVED PROJECTS

PROJECT TITLE: Accelerating the Language Development of Saudi Autistic Children using LENA (Language ENvironment Analysis) Systems: A Pilot Study

This study is the first validation and experimentation study of the Language ENvironment Analysis (LENA) Systems in the Arabic language. This study's goal is for the technology to be available for researchers and clinicians in Saudi Arabia and the Middle East to be used in early intervention and assist in the diagnosis of children with ASD.

ACHIEVEMENTS

- The first phase of the LENA study has been submitted to IMFAR 2015 (International Meeting for Autism Research).
- Reports have been submitted to ORA and KACST.
- Approved for six months extension of the project.
- Final report is expected to be submitted in January 2016.

PROJECT TITLE: Analysis of Neuroanatomic and Neurofunctional Substrates in Autism Spectrum Disorder

This project is in collaboration with Healthcare Belgium Foundation and aims to use NMR imaging techniques (i.e. conventional magnetic resonance (MRI), functional magnetic resonance (fMRI) and diffusion tensor imaging (DTI)) to study the neurofunctional and neuro-anatomic substrates of various autism spectrum disorders. These techniques are being applied to a group of ASD patients, a group of siblings and parents of these patients and to a group of healthy volunteers. The groups will be comparable with respect to age, sex and intelligence level. In addition, the team will attempt to divide the groups using behavioral, neurocognitive and biological variables, which, according to scientific literature on the topic, may form the endophenotypes for autism.

ACHIEVEMENTS

- All equipment for this project have been already purchased and delivered at the center.
- Technicians from Belgium group have been rescheduled to finalize the installation of software in November 2015.

PROJECT TITLE: Characterizing Genetic Abnormalities in Autistic Spectrum Disorder (ASD) Patients in Saudi Arabia

This multidisciplinary multicenter study aims to investigate the genetic basis of ASD patients in Saudi Arabia using genome-wide linkage analysis of ASD families with 3 or more affected individuals. This is achieved by using microarray-based genotyping in combination of candidate gene screening or exome sequencing. 100 Simplex cases will also be studied using a homozygosity-based approach to identify underlying genes and mechanisms. The latest technology is being used in order to gain insight in to the genetics of these disorders and eventually understand the function of the genes and the role of the proteins in the biological system. Identifying the underlying genetic causes of such disorders will help in improving clinical diagnosis, genetic testing and counseling for affected individuals and families in Saudi Arabia.

ACHIEVEMENTS

- Currently there are over 100 families recruited for the project.
- Submitted and accepted for the Abstract presentation March 2015.

- The panel has been agreed to be ready by December 2015.

PROJECT TITLE: The Effect of Responsive Teaching on Mothers and Young Children with Autism in Saudi Arabia

This project is a response to KSCDR and CFAR research focus area Fostering Advanced research and cutting-edge technology with the following objectives: to compare the effectiveness of RT and a parent support group on the cognitive, language and social emotional functioning of children with Autism over a 12 month period of time, compare the impact of RT and Parent Support Groups on mothers' style of interaction and children's pivotal behaviors over a 12 month period of time, to assess how mothers' style of interaction and children's pivotal behavior mediates the developmental and social emotional improvements children make in both intervention groups.

ACHIEVEMENTS

- Conducted lectures for families and professionals May 2015.
- We have translated instruments and intervention materials into Arabic version, such as Maternal Behavior Rating Scale (Revised - 2008) and Child Behavior Rating Scale (Revised, 1998), and Denver II.
- Obtained materials for this project such as 2 TVs, 2 cameras, 1 laptop, ADOS manual.
- Achieved some necessary assessment using Autism Diagnostic Observation Scale(modules 1 and2) as assessed by a certified ADOS examiner from WPS and has six years experiences with ADOS, we have assessed 30 cases by ADOS and still working on other 30 cases.
- Provided training of Interventionists. RT provided by interventionists employed through Prince Sultan for Related services in East Part of Riyadh from April 25 to 8 May 2015. These interventionists received 4 weeks of training (two 2 week on-site training sessions) from, Mahoney, and Merza related to: (1) RT rationale, (2) use of RT strategies, and (3) how to work with parents to learn and implement these strategies.
- RT interventionists pilot tested curriculum with one family. Mahoney reviews videotapes of pilot sessions to determine whether interventions can be certified as IT providers.

PROJECT TITLE: Public Awareness Toward Autism & It's Common Believes in Saudi Arabia (2015 new approved project)

The project's objectives are: to identify public awareness and perception of autism; including common perception of autism, to find ways of raising awareness and comparing the source of knowledge and the barriers facing children with autism.

- Ongoing collection of data through online link and manual questionnaires.
- Finalizing collected data and manual questionnaires to be entered and analyzed by autism Research team using Survey Monkey.

CFAR COLLABORATIVE PROJECTS

The international collaboration has been built on the well-established Networks of KFSHR&RC AND KSCDR.

The main international collaborators are: Autism Speaks, University of North Carolina, Chapel Hill, UC Davis, MIND Institute, University of California, University of Nevada, Reno, LENA foundation, Harvard, Johns Hopkins and Special Education & Communication Disorder, San Francisco State and

we have achieved renewal of service agreement for our collaborators. In addition we are expanding our national and regional collaborations.

The national collaboration, the first steps in working with the various organizations and centers dealing with Autism in Saudi Arabia was to build communication channels, joint meetings and collaborative projects. We built on the previous national meetings and efforts by the Autism Program at King Salman Center for Disability Research (KSCDR), which enabled us to get access to and built relationships with multiple centers and professionals from various areas. In addition, we worked closely with the Charitable Autism Families' Society by holding multiple meetings to understand families' needs, viewpoints and to solicit involvement in research and development efforts. Currently we are in collaboration with: Hessah Bint Ahmed Alsudery Foundation, King Salman Center for Disability Research, Charitable Society of Autism Families., Jeddah Autism Center, King Saud University - College of Applied Medical Sciences - Department of Rehabilitation Sciences and Ministry of Education, Special Education Department – Riyadh.

PROJECT TITLE: Factors Associated with the Use of Autism Services in Saudi Arabia, Public Awareness Toward Autism & Its Common Beliefs in Saudi (2015 new approved project)

This project was initiated by Fahad Alnemry and was undertaken to address the gap in the literature and provide recommendations to policy makers and services providers in the KSA to improve the services of children with ASD and their families. CFAR supported this project to expand the study that aimed to answer the following demands: What services do children with ASD in the KSA receive and what factors are associated with the utilization of these services.

ACHIEVEMENTS

- This study was accepted and presented at the International Meeting for Autism Research in Salt Lake City, Utah in May 2015.
- Finalizing materials for publication.

PROJECT TITLE: Oral Medicine Health Care and Challenges Facing Dentists and ASD Families at Dental Clinics in KSA (2015 new approved project)

Due to challenges facing Dentists difficulties in ASD, the CFAR is in collaboration with Riyadh College of Dentistry and Pharmacy with ASD to identify the following: difficulties facing ASD families in Dental clinic, families' awareness about oral health important and dentists' awareness about ASD.

ACHIEVEMENTS

- Questionnaires have been distributed and received a total of 320 responses.
- Submitted proposal for IMFAR 2016.

PROJECT TITLE: Applied Behavioral Analysis Program (ABA) - in Collaboration with University of Nevada, Reno

ABA is the most scientifically approved and widely used method in training children across all age groups with ASD or other behavioral or developmental disorders in the Western World. There are, however, very few trained and certified ABA therapists in the Kingdom. Moreover, there is no active Training or Certification Programs in the Kingdom or the region

ACHIEVEMENTS

- First phase of the training is done and the second phase has been already started in September 2015.
- The first batch of the ABA students is expected to graduate in August 2016.
- Master's degree agreement is for legal final review.
- Conducted lectures of ABA for specialists and families.
- Achieved approval for two service agreements (BCBA Sequence II and Practicum Training Service II)

PROJECT TITLE: ADAPT Technology: (Using Technologies with two applications)

There are many devices that have been used over the last two decades to aid in communication. Initially these were large devices then progressed to be hand-held ones. The dedicated device for communication has many limitations including the ability to develop open source software and applications. They are also very expensive (10-25,000 USD per device). With the introduction and widespread availability and use of handheld touch devices (iPAD, iPHONE, Android Touch Tablets from various manufacturers), the idea of using these multi-use devices as a reasonably price alternatives to dedicated devices developed, opening up a new world of communication, learning and social possibilities for autistic children. These devices will not cure Autism, but it will improve their communication and social skills in addition to aiding them in learning and academics. This project has three applications such as: Ages/Stages Questionnaire, Developing Arabic Application (2 Communicate) and Initializing for Translating an Application through the collaboration with Moazzaz Company in Canada. Workshops and lectures for professionals and families have been conducted.

ACHIEVEMENTS

- Conducted presentation at Security Forces Hospital.
- Done from translating the ASQ-3 questionnaires and it's now for adaptation editing.
- Starting to recruit patients (ASD siblings from CFAR).
- Waiting for approval of proposal from Security Forces hospital for the ASQ Research.
- Working with Prince Fahad Bin Faisal bin Turki and EJADAH Company for the Arabic application. The phases 1 and 2 of the applications have been finalized and ready for utilization once STC responded for the sponsorship.
- Accomplished application for children with Damam University and they are using it now.

PROJECT TITLE: Saudi National Center for ASD Program Development (SNCPD-ASD)

In collaboration with University of North Carolina with a goal to establish a network of connected local Autism centers working together with our major international collaborators to promote the use of Evidence- Based Practices for Children and Youth with Autism and their families in Saudi Arabia. This will be a continuous training via internet based learning modules (iLearning), video vignettes and frequent video-conferences with the main training site in the USA. This is a collaborative program with Autism Speaks, New York, USA (the largest Autism Advocacy and Research Funding Agency) and the National Professional Development Center (NDPC) University of North Carolina- Chapel Hill, North Carolina, USA (which works together with the MIND Institute of UCD- Davis and the Waisman Center at the University of Wisconsin). Currently, the NPDC is working with 12 states in the US to establish professional development programs that support the use of evidence based practices at the early intervention, preschool elementary, and middle school.

ACHIEVEMENTS

- Achieved the pilot phase with Jeddah Autism Center (trainings and supervision for the teachers were done).
- Attained collaboration with School 51 (we train and supervising teachers to use Evidence Based Practice).
- Achieved renewal of service agreement with University of North Carolina and we'll be sending 3 CFAR specialists to UNC for extensive training.
- Proposed Tatweer agreement and it's now for approval.
- Submitted proposal for IMFAR, "Using technology to promote the implementation of evidence-based practices in the United States and internationally for learners with ASD".
- Developing website to upload all the translated materials 70% done and ready for uploading.

PROJECT TITLE: Occupational Therapy (Sensory Integration)

ACHIEVEMENTS

- Submitted proposal for collaboration with WPS for the SPM and SPM-P assessment and questionnaire tools for Occupational Therapist, to be translated in Arabic.
- Initialized the Translation of book "Building Bridge through sensory Integration 3rd edition" is expected to be published Feb. 2016.
- Training and supervision for Riyadh Centre to establish and provide OT services for their enrolled cases & for them to establish a sensory integration room.
- Conducting Occupational Therapy training and lectures at school 51.
- Working on collaboration with USC for CFAR to be the regional training center for sensory integration therapy.
- Supervising intern Occupational Therapy students from King Saud University, Occupational Therapy department.
- Supervising and training intern Occupational Therapy students in Mother of Faisal Autism Center.
- Establishing sensory integration room in school 51.

PROJECT TITLE: Developing and Publishing the Standard Autism Diagnostic Tools (ADI-R)

Although the diagnosis of Autism might seem easy in some individuals, there are many challenging cases especially when in young children or when the symptoms are mild. Confirming the diagnosis and defining the phenotype and severity is of paramount importance for intervention programs and to monitor improvement. It is also quite essential for any research projects, whether basic or clinical. The gold standard diagnostic tools are either interview-based (such as the Autism Diagnostic Interview - Revised (ADI-R)) or Observational (such as the Autism Diagnostic Observational Schedule (ADOS)).Training workshop in the gold standard diagnostic tools namely ADOS and ADI-R were sponsored by CFAR.

ACHIEVEMENTS

- The official ADI-R materials of the book have been finalized and sent to official publisher to be published within this year.
- The interview booklet and algorithm form is ready and printed.
- Achieved 5 of CFAR specialists are clinically certified in ADI-R.

PROJECT TITLE: Early Start Denver Model (ESDM)

We have achieved seven CFAR therapists obtained certification in the Early Start Denver Model

(ESDM), in which they demonstrated the ability to implement ESDM techniques reliably and according to high standards set by leading ESDM therapists. ESDM intervention is a relationship-based intervention provided in the home by trained therapists and parents during natural play and daily routines and certification ensures that a certified professional has the knowledge and skills to successfully use the teaching strategies with children with autism.

ACHIEVEMENTS

- Achieved the first center that is specialized in providing ESDM intervention in the Middle East.
- Established collaboration with UC Davis Mind Institute and Autism Speaks, New York, to translate the adaptation to Arabic and to publish the ESDM book.
- Achieved six specialists are now ESDM certified.
- We have reached 3,500 hours of Early Intervention with ASD children.

PROJECT TITLE: Beacon Compass Project (2015 new approved project)

This project is in collaboration with King Salman for Disability Research. The important mission of this project is to establish a model for the societal-level support of individuals with learning disabilities by defining, adapting, and implementing cutting-edge advances in pedagogy and assistive technology and supporting teachers and professionals in the schools and higher education institutes; which will provide Saudi citizens with learning disabilities authentic opportunities to achieve their greatest potential. As part of the Learning Disabilities Strategic Plan, the Beacon Compass program was established, in collaboration with Beacon College. Beacon College in Leesburg, Florida is the first college in the United States to offer a bachelor's degree programs exclusively to students with learning differences and have one of the highest four-year graduation rates in the country. The aim of the Beacon Compass Program, an intensive 4-week summer program, is to provide students a golden opportunity to embark on a journey of self-discovery, learning and independence. Fittingly, the symbol of the program is a compass – a device designed to help people navigate the world.

ACHIEVEMENTS

- Six Saudi students were recruited to be part of a pilot program that launched July 21, 2015. In cooperation with Beacon College, Florida, a thorough program was devised to incorporate the latest cutting-edge pedagogical strategies for individual learners. The program included TOEFL training sessions, STEM classes (Science, Technology, Engineering, and Math), leadership and team building, learning methodologies, and research methods. In addition to the academics, the students were given the opportunity to experience "life on campus" and the mature responsibilities they'll face as independent young adults with the assistance of Beacon students.
- Parents of the students were very happy with the program and the influence it had on their children. Many noticed an increase in their sons' self-confidence, independence, communication, and positive attitude regarding their disabilities. They made long lasting friendships and now have dreams of continuing their education and graduating from college.
- Officials in the city of Leesburg showed their enthusiasm and support for the program and set up public and private events to welcome the students and the staff. Dr. George Hagerty, the president of Beacon College, and KSCDR representatives met with the Mayor of the city of Leesburg, Elise A. Dennison, and were honored with a proclamation ceremony.

- Plans and accommodations have been made for the Beacon College Psychologists to travel to Saudi Arabia in December 2015, in order to meet with the parents and discuss the results of the evaluation as well as share the report and summary of each student's progress areas of strength and improvement as well as accommodations that will significantly help in their personal and academic environments.

CFAR 2015 WORKSHOPS AND LECTURES

JANUARY 2015

- Providing weekly lectures of Occupational Therapy for King Saud University.
- Sensory Integration strategies workshops for families and professionals at KFSH&RC.
- Presented lectures for Applied Behavioral Analysis (ABA) workshop at KFSH&RC.

FEBRUARY 2015

- Snoezelen Workshop with international speakers at KFSH&RC.
- Conducted presentation for Dentists (Riyadh College) about the ASD and how to deal with challenges behavior.
- Presented four lectures for Jeddah Autism Center.
- Provided lectures at school 51.
- Two days' workshop for MozzazCare.
- Pep 3 Workshop (3 days) at Jeddah Saudi Autism Society.
- Pep 3 Workshop 3 days at Prince Faisal's Mothers in Riyadh.

MARCH 2015

- Presentation at ICAN conference at Faisaliah hotel.
- Conducted four days' workshop for Autism Diagnostic Interview Review (ADI-R)
- Three months Weekly lectures for Sensory Integration for the teachers of school 51, held in CFAR.
- Early Start Denver Model Workshop for professionals and families at KFSH&RC.

APRIL 2015

- Sensory Integration two days workshop for Professionals in collaboration with Ministry of Health in Al Ghasim.
- Sensory Integration strategies workshops for families and professionals at KFSH&RC.
- Autism awareness activities.

MAY 2015

- CFAR Poster Presented Behavior Analysis International (ABAI) Conference in San Antonio Texas, USA.
- Participated for 2nd Saudi International Exhibition for People with Disability Requirement, Riyadh Convention & Exhibition Center.
- Conducted workshops for "The Effect of Responsive Teaching on Mothers and Young Children with Autism in Saudi Arabia"

AUGUST 2015

- Provided presentation and lectures for the Applied Behavioral Analysis Program (ABA) at KFSH&RC.

SEPTEMBER 2015

- Conducted workshop for Applied Behavioral Analysis (ABA) at KFSH&RC.

OCTOBER 2015

- PEP 3 workshops for 3 days at Prince Faisal's Mothers in Riyadh

November 2015

- Presented for Mother of Faisal Autism Center, Riyadh (MFAC) for presentation 2015

EXISTING PUBLICATIONS

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- Kaya, N., Colak, D., AlBakheet, A., Al-Owain, M., Abu-Dheim, N., Al-Younes, B., Al-Zahrani, J., Mukaddes, N.M., Dervent, A., Al-Dosari, N., Al-Odaib, A., Kayaalp, I.V., Al-Sayed, M., Al-Hassnan, Z., Nester, MJ., Al-Dosari, M., Al-Dhalaan, H., Chedrawi, A., Gunoz, H., Karakas, B., Sakati, N., Alkuraya, F.S., Gascon, G.G, Ozand, P.T. (2012). A novel X-linked disorder with developmental delay and autistic features. *Ann Neurol*. Apr; 71(4),498-508.
- Colak, D., Al-Dhalaan, H., Nester, M., AlBakheet, A., Al-Younes, B., Al-Hassnan, Z., Al-Dosari, M., Chedrawi, A., Al-Owain, M., AbuDheim, N., Al-Alwan, L., Al-Odaib, A., Ozand, P., Sait Inan, M., Kaya, N. (2011). Genomic and transcriptomic analyses distinguish classic Rett and Rett-like syndrome and reveals shared altered pathways. *Genomics*. Jan; 97 (1),19-28
- Homozygosity analysis and sequencing in a Saudi Arabian highly inbred family with ASD. Adi A, Tawil B, Aldosari M, Nester M, Ghannam M, Meyer B, Al Tassan (WFSBP Congress 2013) (oral presentation)
- Exome Sequencing in a Multiplex Family with Autistic Spectrum Disorder. Tawil B, Adi A Aldosari M, Nester M, Aldhalaan H, Naim E, Monies D, Ghannam M, Meyer B, Moniew D, Al Tassan N. (FENS 2012 poster.
- Whole Exome Sequencing in a Multiplex Family with Autistic Spectrum Disorder. Tawil B, Adi,A, Aldosari M, Naim E, Almuslamani A, Nester M, Ghannam M, Meyer B, Monies D. Al Tassan N. (FENS 2012) poster.
- Screening for Variants in the PTEN gene in ASD Patients in Saudi Arabia. Adi A, Tawil B, Aldosari M, Almuslamani A, Nester M, ghannam M, Meyer B, Al Tassan N. IMFAR 2012.
- Loss of Heterozygosity in Saudi Patients with ASD. Shinwari J, Aldosari M, Almuslamani A, Adi A, Khalil D, Abu Dheim N, Nester K, Ghannam M, Meyer B, Al Tassan. IMFAR 2011, 11-14 May. (poster).
- Al Tassan, Shinwari J, Al Sharif L, Khalil D, Almuslamani A, Khalak H, Ghannam M, Meyer B, Nester M, Aldosari M. copy Number Variation and Loss of Heterozygosity in Saudi Patients with aSD. 60yh annual meeting of the American Society of Human Genetics, Washington, USA 2-6 Nove 2010. (poster).
- Aldosari M, Al-Sharif L, Khalil. D, Shinwari J, Almuslamani A, Al Tassan N. Mapping of a Loci for Autistic Specturm Disorder on Chromosomes 7q31.31-31.33 and 9q21.33-q22.2. IMFAR 2010 meeting (poster).
- Almuslamani A, Al-Sharif L, Khalil. D, Shinwari J, Khalak H, Al Tassan N, Meyer B, Nester M, Aldosari M. Clinical and Neuropsychological fprofile; Autism in Saudi Arabia: A systematic approach. IMFAR 2010 meeting. (poster)
- Aldosari M, Al-Sharif L, Khalil D, Shinwari J, Almuslamani A, Al Tassan N. Mapping of a Loci for Autistic Spectrum Disoder on Chromosomes 7q31.31-31.33 and 9q21.33-q22.2. ANN 2010 meeting. (poster).
- Al Tassan, Characterizing Genetic Abnormalities in Autistic Spectrum Disorder (ASD) Patients in Saudi Arabia, 3rd International Conference on

Disability and Rehabilitation, Rigaydh, Saudi Arabia, 22-25 March 2009. (Presentation).

- Proposal for National Autism Diagnostic, Intervention and Rehab Center.
- The publication of ADIR and scheduled training workshops.
- The publication of ESDM - In process
- Memorandum of Understanding between Center for Autism and Ministry of Education, Jeddah Autism Center, Mozaz and Autism Families Society.
- Accelerating Novel Candidate Gene Discovery in Neurogenetic Disorders through Whole-Exome Sequencing of Prescreened Multiplex Consanguineous Families, in collaboration with Neurosciences department. Co-author: Dr. Hesham Aldhalaan

CLINICAL STUDIES AND EMPIRICAL ETHICS DEPARTMENT

CLINICAL STUDIES AND EMPIRICAL ETHICS

DIRECTOR

Muhammad M. Hammami, MD, PhD, FACP, FACE

ADMINISTRATIVE SUPPORT STAFF

Abdelraheem Abdel Galeel M. Ahmed

Maria Lourdes E. Bautista

THE CLINICAL STUDIES AND EMPIRICAL ETHICS DEPARTMENT CONDUCTS clinical, pharmacokinetic, and empirical ethics studies and educates and trains research professionals. It also provides infrastructure for qualified clinical and empirical ethic research by members of KFSH&RC and aspires to promote collaboration among basic scientists and clinical investigators. The Department has been recognized as a bioequivalence center by the Saudi Arabian Ministry of Health and the Health Ministers of the Gulf Cooperative Council States. Members of the Department are on the editorial board of BMC Medical Ethics Journal, are regular reviewers for international journals, provide direct patient care, and participate in institution-wide educational activities. The Department has three sections: clinical studies, empirical ethics, and drug analysis laboratory; it hosted environmental health research from 2012 to June 2015.

CLINICAL STUDIES SECTION

HEAD

Muhammad M. Hammami, MD, PhD

STAFF

Eman Ali Al Gaai, CCRP, MHHA *Technical Specialist*

Sophia Jehan De Padua *Clinical Research Coordinator*

Fadoma Abdi Farah *Staff Nurse*

THE SECTION CONDUCTS, FACILITATES THE CONDUCT OF, CLINICAL studies, including bioequivalence studies. Bioequivalence studies compare the rate and extent of absorption of two formulations of the same drug. They help ensure that locally-made generic drugs fulfil regularity requirements and indirectly reduce the cost of medical care.

Educating and training research professionals is at the heart of conducting clinical research that meets international ethics guidelines and scientific standards. The section offers two modules of a semi-annual Clinical Research Professionals' Course:

1) Clinical Studies' Designs, Methods, and Analysis Module (2 weeks) is accredited with 30 CME hours by the Saudi Commission for Health Specialties (SCFHS) and 49.25 CME hours by the American Association of Continuing Medical Education (AACME).

2) Clinical Research Activities Module (1 week) is accredited with 22 CME hours by the SCFHS & 24.5 hours by the AACME.

FACILITY

The facility consists of a research clinic and a waiting area. It is equipped with:

- Phlebotomy chairs
- Crash carts
- Ultrasound Machine (Titan, portable)
- EKG Machine (MAC 5500)
- I-Lyte NA/K/CL Analyzer
- I-Lab 300 Auto chemistry Analyzer
- CBC Coulter Ac.T diff.
- Digital Weighing Scale (Tronix)
- Vital Signs System (Dinamap pro 300v2)
- Life Scan Glucometer

ONGOING RESEARCH ACTIVITIES

PROJECT TITLE: Effect of Vitamin D Oral Supplement on 25 OH Vitamin D levels: A Randomized Controlled Trial
RAC# 2101041, funded by the National Plan for Science, Technology and Innovation, SR 2,000,000

PROPOSAL ABSTRACT: Vitamin D deficiency is common in Saudi Arabia and world-wide. 25 OH vitamin D level is the best indicator of vitamin D status. Vitamin D supplements are available as vitamin D2 or D3, in small daily or large weekly/monthly doses. Controversy continues on the relative potency of vitamin D2 compared to D3 and of daily compared to weekly or monthly doses, in increasing/maintaining total 25 OH vitamin D level. We plan to conduct a blinded, randomized controlled trial to compare the effect of various vitamin D supplements on 25 OH vitamin D levels in healthy adults with starting 25 OH vitamin D level between 20 to 50 nmol/L. We will randomize 800 individuals to one of eight groups: daily dose of 2000 IU D2, 2000 IU D3, or a combination of 1000 IU D2 and 1000 IU D3; 2-weekly doses of 25,000 IU D2 or 25,000 D3 IU; or 4-weekly doses of 50,000 IU D2 or 50,000 IU D3; or a placebo given daily. Treatment will continue for 5 months. The randomization sequence, stratified by body mass index (≤ 30, › 30 kg/m2) and gender (males and non-pregnant females) will be generated using an on line program. Participants as well as personnel involved in the determination of vitamin D/metabolites level and data analysis will be blinded as to the content of the individual participant's assignment. Using a locally validated reversed-phase HPLC method, vitamin D (total and fractionated) and 25 OH vitamin D (total and fractionated) will be measured at baseline, days 1,2,3,4,7,14, and biweekly thereafter. Serum Ca and phosphate levels, and urine Ca and phosphate to creatinine ratios will be obtained at baseline and at 5 months. The primary endpoint is the area under the curve of days 1 to 140 (AUC) of total 25 OH vitamin D levels. The AUC of the placebo group will be used to determine changes in total 25 OH vitamin D levels that are not related to intervention. Secondary endpoints include C_{max} and T_{max} of 25 OH vitamin D, AUC of vitamin D, and the incidence of hypercalcemia and hypercalciuria. The (adjusted) primary endpoint of the three daily regimens, the two 2-weekly regimens, the two 4-weekly regimens, the three vitamin D2 regimens, and the three vitamin D3 regimens will be compared by ANOVA (5 ANOVA tests). Pair-wise comparison will be conducted by unpaired 2-tail t test. The study will establish the relative efficacy of the various oral supplements of vitamin D and whether vitamin D2 supplement adversely affect 25 OH vitamin D3 levels. The information obtained will be important for scientists in the field, managing physicians, and policy makers.

PROJECT TITLE: Interaction Between Drug and Placebo Effect: Randomized Placebo-Controlled Trials May Not Be Accurate in Determining Drug Effect Size
RAC# 2111 001, funded by KFSH&RC

PROPOSAL ABSTRACT: *Background:* The total effect of a medication is the sum of its drug effect, placebo effect (meaning response of placebo), and their possible interaction. Current interpretation of the results of clinical trials (the gold standard in evidence based medicine) assumes no such interaction. Using a novel cross-over balanced placebo design and caffeine as a model drug (KACST ARP-26-45), we have recently shown that a negative interaction does exist; suggesting that the size of the drug effect as currently measured by clinical trials may not be accurate. Due to the novelty of the findings and their important clinical practice and research implications, they need to be confirmed using another drug; and the size of drug effect measured using the novel design need to be directly compared to that measured using conventional clinical trial design. *Design:* A cross-over balanced placebo plus randomized placebo-controlled clinical trial design. *Methods:* 480 adults will be double-blindly randomized to three groups: first generation H-1 receptor antagonist-hydroxyzine (25 mg), placebo, or hydroxyzine+placebo group. The first two groups will receive the assigned intervention described by the investigators as hydroxyzine or placebo, in a randomized crossover design. The third group will receive hydroxyzine and placebo in a randomized double-blind placebo-controlled crossover design. Group assignment will be concealed from volunteers and recruiters. Data collectors will be blinded to group assignment and intervention assignment. Volunteers will be partially deceived to the intervention assignment in the first two groups and blinded in the third group. The interventions to the third group will be also administered blindly. Serum hydroxyzine levels will be determined 3 hours post intervention from all volunteers to verify compliance and help maintain deception/blinding. Seven-hour-area-under-the-curve of drowsiness and dryness of the mouth (on 100 mm visual analog scales) as well as mean percent of time of reporting these symptoms on a dichotomous scale will also be determined. Using ANOVA (the model includes sequence, subjects nested within sequence, period, and intervention as appropriate, as well as baseline value as a covariate), drug, placebo, placebo-plus-interaction, and total effects will be estimated by comparing outcomes (in the first two groups) after receiving hydroxyzine described as placebo to receiving placebo described as placebo, receiving placebo described as hydroxyzine or placebo, receiving hydroxyzine described ad hydroxyzine or placebo, and receiving hydroxyzine described as hydroxyzine to receiving placebo described as placebo, respectively. Drug effect will be also conventionally determined using data from the third group. The placebo effect will be compared to the placebo+interaction effect and the conventionally measured hydroxyzine drug effect will be compared to the novelty measured hydroxyzine drug effect, using independent 2-tail t test.

PROJECT TITLE: Generic Formulations of Commonly-Used, Immediate-Release, Solid, Oral, Drugs in Saudi Arabia: Interchangeability & Post Marketing Quality

RAC# 2101100, funded by the National Plan for Science, Technology and Innovation – SR2,000,000

PROPOSAL ABSTRACT: Generic formulations of prescription drugs can, through their relatively lower cost, improve healthcare as long as they maintain their registration-quality and public trust. On the other hand, the market availability of several generic formulations raises a concern regarding their interchangeability, despite being proven to be individually therapeutically interchangeable with their corresponding innovator formulation. We propose to assess the quality and therapeutic interchangeability of generic formulations in the drug market of Saudi Arabia, using fifteen, commonly-used, oral, solid, immediate-release,

and non-combinational drugs.The following drugs have been identified from the Saudi National Formulary (September 2006) as having, among oral, immediate-release, non-combinational drugs, the highest number of formulations (they have each 15 to 47): ciprofloxacin, ranitidine, amoxicillin, paracetamol, atenolol, cephalexin, ibuprofen, diclofenac, metformin, omeprazole, metronidazole, enalapril, clarithromycin, amlodipine, and fluconazole. In the first set of studies and for each drug, a four-treatment, four-period, four-sequence, crossover bioequivalence study will be conducted on the innovator and three randomly-selected generic formulations. Each study will be designed to have a power of 0.9 to detect bioequivalence, and sampling and wash-out periods of at least 5 to 7 half lives, respectively. Individuals who are identified in the first set of studies as having the large intra-subject variation (bioequivalence parameters ratios of less the 80% or more than 120% for AUC) will be subjected to a second set of studies, in which 2 batches of the reference formulation (including the batch used in the first set of studies) and the generic formulation will be compared in a two-treatment, four-period, two-sequence, replicate design crossover bioequivalence study. Drug levels will be determined by an HPLC or LC-MS-MS method, locally-validated according to the Saudi Arabia Ministry of Health (MOH) and international guidelines. After log transformation, AUC and C_{max} (non-compartmental model) of the formulations will be compared pair-wise by ANOVA. Pair-wise bioequivalence will be tested by 90% (and 95%) confidence interval of ratios and Schuirmann's two one sided t-tests for the 70-143, 80-125%, and 90-112% ranges. The following (among others) will be determined: (1) the prevalence of generic formulations that are not bioequivalent to their innovator formulation; (2) the prevalence of the phenomena that two generics of the same innovator formulation are not bioequivalent to each other; (3) the percentage of individuals with large intra-subject variation despite the presence of average bioequivalence between the two formulations; and (4) how much of the large intra-subject variation in 3 above is true or related, in part, to product failure, random error, or subject-by-formulation interaction; and how it compares to intra-subject variability when two batches of the innovator formulation are compared. The studies will be conducted according to the regulations of the MOH and in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP) Guidelines, and Good Laboratory Practice (GLP) Guidelines. The results of this project are expected to provide clinically-and regulatory-critical information on the post-marketing quality of generic formulations on the Saudi market and on the extent of the interchangeability of generic formulations in general.

PROJECT TITLE: Bisphenol Determination Urine
RAC# 2141 021, funded by KFSH&RC

PROPOSAL ABSTRACT: Bisphenol A (BPA) is a manufactured chemical that is present in many types of plastic bottles, food and beverage cans, resins, and thermal papers since 1960s. Many people are exposed daily to low levels of BPA that leaches into water and food from their plastic containers including baby bottles. BPA exposure levels in humans was not evaluated in Saudi Arabia, according to the investigator's knowledge. In order to identify the extent of BPA exposure we plan to conduct a cross- sectional exploratory study in healthy volunteers. 1000 healthy adult males and non-child bearing females, 18 to 60 years old, attending as patient companions or employees of the KFSH&RC will be enrolled. After the subject undergoes a screening examination, which will include the following: demographics, medical history, height/weight, blood pressure, temperature, the researcher will complete the

questionnaire about exposure to BPA-containing product through individual interview, and then the subject delivers a spot urine sample. This study is designed to explore exposure level of BPA in Saudi Arabia using urine level biomarker of BPA as the primary end point. *The aims of this study are to:* to determine BPA exposure level in healthy research subjects; to determine the association between urinary BPA and potential dietary exposure; to determine the association between urinary BPA and demographic data; and to develop and locally validate a BPA in urine assay using liquid chromatography. The information obtained will be important for scientists in the field, managing physicians, and policy makers.

PROJECT TITLE: The Placebo Effect may Involve Modulating Drug Bioavailability
RAC#2101105, funded by KFSH&RC

PROPOSAL ABSTRACT: The total effect of a medication is the sum of its drug effect, placebo effect (meaning response of placebo), and their interaction. Current interpretation of clinical trials (the gold standard of evidence-based-medicine) assumes no interaction, and the mechanism(s) underlying such interaction have not been fully explored. One possibility is that the placebo effect may modulate drug bioavailability. Using caffeine as a model drug (KACST ARP-26-45), we have recently shown that the placebo effect of caffeine ingestion prolongs caffeine half life. Due to the novelty of this finding and its important clinical practice and clinical practice and clinical research implications, it needs to be confirmed in another set of subjects and extended to additional drugs. *Design:* Balanced cross-over, single-dose, two-period, two-group design comparing caffeine, paracetamol, cephalexin, and ibuprofen described as such (overt) to the same medication described as placebo (covert). *Methods:* 32, 50, 50 and 30 healthy adult volunteers will be enrolled in the caffeine (300 mg), paracetamol (500 mg), cephalexin (500 mg), and ibuprofen (400 mg) cross-over studies, respectively. Volunteers will be partially deceived to the intervention assignment (i.e., in the covert arm). Serum levels of each drug will be blindly determined by locally validated HPLC assays. Plasma half-life (primary outcome) as well as C_{max}, T_{max}, and AUC (secondary outcomes) of each drug will be determined and analyzed by ANOVA. The model will include group, subjects nested within group, period, and intervention (overt vs. covert drug). In a secondary analysis, the difference between covert and overt drug in the means of the long-transformed values of the pharmacokinetics end points will be analyzed by 90% confidence interval. *Utility:* The results of the study are expected to further our understanding of the mechanism of action of a widely used medical intervention, i.e., placebo. The results will be important for both clinical practice and clinical research.

EDUCATIONAL ACTIVITIES

- 17th Clinical Research Professionals' Course - Clinical Studies' Designs, Methods and Analysis (26–30 April 2015)
- 17th Clinical Research Professionals' Course - Clinical Research Activities (10–14 May 2015)
- 18th Clinical Research Professionals' Course - Clinical Studies' Designs, Methods and Analysis (15–26 November 2015)
- 18th Clinical Research Professionals' Course - Clinical Research Activities (29 November–03 December 2015)

PUBLICATIONS

- Hammami Muhammad, Duaiji Najla, Mutairi Ghazi, Aklabi Sabah, Qattan Nasser, Abouzied Mohei, Sous Mohamed. Case report of severe Cushing's syndrome in medullary thyroid cancer complicated by functional diabetes insipidus, aortic dissection, jejunal intussusception, and paraneoplastic dysautonomia: Remission with sorafenib without reduction in cortisol concentration. BMC cancer, 9 September 2015, Vol.15(1), pp.624

FEE-FOR-SERVICE

- 17th CRPC-Clinical Studies' Designs, Methods and Analysis SR 31,200
- 17th CRPC-Clinical Research Activities SR 16,800
- 18th CRPC-Clinical Studies' Designs, Methods and Analysis SR 45,800
- 18th CRPC-Clinical Research Activities SR 29,600

EMPIRICAL ETHICS SECTION

HEAD

Muhammad M. Hammami, MD, PhD

STAFF

Eman Ali Al Gaai, CCRP, MHHA *Technical Specialist*

PERCEPTION, RATHER THAN REALITY, OFTEN CONTROLS BOTH THE generation and resolution of ethical issues. Although perception ought to govern the generation of ethical issues, reality (rather than perception) must often govern their resolution. Thus, there has recently been a move toward evidence-based bioethics similar to that in medicine. Several widely held ethical views that were based on normative ethical perspectives did not stand empirical testing. The section offers one module of the semi-annual Clinical Research Professionals' Course: Experimental and Philosophical Approaches to Ethics: Application to Clinical Research Module (1 week) is accredited with 22 CME hours by SCFHS and 29.50 CME hours by the AACME.

ONGOING RESEARCH ACTIVITIES

PROJECT TITLE: Preventive Interventions: Extent of Knowledge, Preferences, and Current Practices
RAC#2101105, funded by KFSH&RC

PROPOSAL ABSTRACT: Patients' autonomy in making medical care decisions have a central value in medical ethics since they are in the best position to determine what would be good and bad for them and there is no danger of harming others. Several studies reported large percentages of patients expecting to be informed of the numerical benefit of preventive interventions before making a decision to start but there is little, if any, information on patients' expectations of preventive interventions' benefits from this region. This proposal intends to determine patients' perceptions (estimations) and preferences (expectations) on preventive medications for cardiovascular disease (CVD patients) and breast cancer screening (breast cancer patients) in addition to their companion. We plan to survey the opinion of the "public" (patient and healthy subject) attending the King Faisal Specialist Hospital and Research Centre on the level of acceptable minimum benefit of preventive interventions, the role of preventive interventions (perception of norm vs personal preferences) and type of information provided on preventive interventions which reflects current practice or personally preferred. Data will be collected from 600 individuals using self- or investigator- administered questionnaire that have been developed by the author. The results are expected to broaden the knowledge base and enlighten physicians and policy makers to improve their service.

PROJECT TITLE: Saudis End-of-Life Priorities: Patterns and Extent of Sharing with Family Members and Physicians
RAC #2081 057, funded by KFSH&RC

PROPOSAL ABSTRACT: Human care at end-of-life (EOL) depends to a large extent on helping patients die the way they prefer. Patients have different EOL priorities which they hold at different hierarchy. These priorities are often not made known to either the family or the physicians, undermining surrogate decision making. Using the Q methodology, we plan to discover patterns of EOL priorities in Saudis. We will also compare these patterns between family members and between medical professionals and non-medical professionals. A Q set of potential EOL priorities that has been developed by the investigators will be piloted on 10 Saudi medical professionals and 10 Saudi non-medical professionals, for clarity, redundancy, inclusivity, balance, and reproducibility. One hundred Saudi adult pairs (husband-wife, parents-children) will be asked to sort the Q set twice, first according to their own priorities and second according to what they think the priorities of their pairs are. In addition, 100 Saudi medical professionals will be asked to sort the Q set twice according to their own priorities and according to what they think the average Saudi patients' priorities are. The study is expected to provide physicians and policy makers with vital information on EOL priorities of Saudis. It will identify Saudi view(s) and contribute to global bioethics on EOL as well.

PROJECT TITLE: Modelling Ethical Resolution: Mapping Points of Ethical Equilibrium
RAC#2060 004, funded by KFSH&RC

PROPOSAL ABSTRACT: Making decision on ethical issues is based on beliefs and on balancing several ethical values/principles. The different ways individuals of different backgrounds use and balance ethical principles have not been well defined. We propose to use Q methodology to identify models of ethical decision-making and points of ethical equilibrium in regards to three controversial bioethical topics including the acceptance of placebo use

in medicine. Several Q-sets will be constructed and examined for reliability and validity. The extent people use ethical principles other than those described in the four-principles-plus-scope approach (i.e., respect for autonomy, beneficence, non-malificence, and justice) will be examined. The association of various demographic factors with the identified models and the effect of formal ethical education will be studies. We will also explore the stability of the identified models/points of equilibrium over time, within demographic groups, and across topics. The results are expected to have important contributions to empirical ethics of ethical resolution and to evidence-based ethics regarding current bioethical issues. It may show that beliefs aside, ethical resolution models/ points of equilibrium may not be different across nations or segments of society. It will also provide empirical evidence for or against the adequacy of the simplified four-principles-plus-scope approach in biomedicine.

EDUCATIONAL ACTIVITIES

- 17th Clinical Research Professionals' Course-Experimental and Philosophical Approaches to Ethics: Application to Clinical Research (3-7 May 2015)

PUBLICATIONS

- Muhammad M Hammami, Eman A Al-Gaai, Safa Hammami, and Sahar Attala Exploring end of life priorities in Saudi males: usefulness of Q-methodology. BMC Palliative Care (2015) 14 : 66

FEE-FOR-SERVICE

- 17th CRPC - Experimental and Philosophical Approaches to Ethics: Application to Clinical Research SR 18,000

DRUG ANALYSIS LABORATORY

HEAD

Muhammad M. Hammami, MD, PhD

STAFF

Syed N. Alvi, PhD *Scientist*
Ahmed Yusuf *Research Associate*
Rajaa Hussein *Research Associate*
Reem Alswayeh *Research Associate*
Nada Hashim *Research Assistant*
Saleh Al Dgither *Research Assistant*

THE LABORATORY PERFORMS DRUG ASSAY METHOD DEVELOPMENT and validation, therapeutic drug monitoring, and pharmacokinetic analysis. It has developed and validated over 50 assays.

The section offers a Semi Annual Liquid Chromatography: Concepts and Hands-On Training Course. The course is designed to provide an in-depth review of chromatography: theoretical foundation, equipment involved, selection of column, detector, mobile phase, and method development and validation to determine drug levels in biological matrices. The course also covers laboratory safety and quality improvement.

FCILITY

The laboratory is equipped with:

- Five Waters Alliance HPLC Systems and multiple detectors: Ultraviolet (UV), Photodiode Array (PDA), Fluorescence (FL), Electrochemical (ECD)
- Hanson SR8-Plus Dissolution Test System
- Ultra Performance Liquid Chromatography (Aquity)
- Micro Mass Quattro Mass Spectrometer (LC-MS/MS) System
- Waters® Xevo® TQD (LC-MS/MS) system

ONGOING RESEARCH ACTIVITIES

PROJECT TITLE: Vitamin D Content in Fortified Liquid Milk in Saudi Arabia: A Cross-sectional Study
RAC# 2100014, funded by KFSH&RC

PROPOSAL ABSTRACT: A reliable high performance liquid chromatography (HPLC) assay for simultaneous determination of vitamin D2 (VD-2) and vitamin D3 (VD-3) levels using indeno (1,2,3-CD) pyrene as an internal standard (IS) was developed and validated. The relationship between the concentration of VD-2 and VD-3 in milk and peak area ratio (VD-2 and VD-3) to the IS was linear over the range of 100 - 2400 IU/L. Mean extraction recoveries of VD-2 and VD-3 from milk samples were over 90%, and 62% for IS. The stability of VD-2 and VD-3 in milk was determined under various storage conditions. The method is being used to assess VD-2 and VD-3 levels in milk samples c available in the market of Riyadh.

PROJECT TITLE: Effect of Vitamin D Oral Supplement on 25 OH Vitamin D levels: A Randomized Controlled Trial
In conjunction with Clinical Studies Section

PROJECT TITLE: Interaction Between Drug and Placebo Effect: Randomized Placebo-Controlled Trials may not be Accurate in Determining Drug Effect Size
In conjunction with Clinical Studies Section

PROJECT TITLE: Generic Formulations of Commonly-Used, Immediate-Release, Solid, Oral, Drugs in Saudi Arabia: Interchangeability & Post Marketing Quality
In conjunction with Clinical Studies Section

PROJECT TITLE: Bisphenol Determination Urine
RAC# 2141 021 (in conjunction with Clinical Studies Section

PROJECT TITLE: The Placebo Effect may Involve Modulating Drug Bioavailability
In conjunction with Clinical Studies Section

EDUCATIONAL ACTIVITIES

- 12th Semiannual Liquid Chromatography: Concept And Hands-On Training Course (06-10 December 2015)

PUBLICATIONS

- Reem Al Swayeh, Syed N. Alvi, Muhammad M Hammami. Rapid determination of hydroxyzine concentration in human plasma by high performance liquid chromatography. *World Journal of Pharmacy and Pharmaceutical Sciences*, 07/2015; 4(7):1657-1667.
- Ahmed Yusuf, Syed N Alvi, Muhammad M Hammami. Development and validation of RP-HPLC method for the determination of rosiglitazone in human plasma. *World Journal of Pharmacy and Pharmaceutical Sciences*, 4:3 (2015) 231-242.
- Syed N Alvi, Muhammad M Hammami. A validated reversed-phase HPLC method for the determination of hydrochlorothiazide in human plasma. *American Journal of Pharm Tech Research*, 5:2 (2015) 445-545.

- Syed N Alvi, Chafica El Tabache, Muhammad M Hammami. Determination of vitamin D in fortified milk by Ultra performance liquid chromatography. *World Journal of Pharmacy and Pharmaceutical Sciences*, 6:4 (2015) 271-281.
- Ahmed Yusuf, Syed N Alvi, Muhammad M Hammami. Development and validation of RP-HPLC method for the determination metformin in human plasma. *World Journal of Pharmacy and Pharmaceutical Sciences*, 4:07 (2015) 128-138.
- Rajaa F Hussein, Muhammad M Hammami. Development of pioglitazone level and its stability in human plasma by HPLC Assay. *World Journal of Pharmacy and Pharmaceutical Sciences*, 4:09 (2015) 11-22.
- Reem Alswayeh, Syed N. Alvi, and Muhammad M. Hammami. Rapid determination of amoxicillin levels in human plasma by high performance liquid chromatography. *World Journal of Pharmacy and Pharmaceutical Sciences*, 07/2015; 4(7):1657-1667.
- Syed N Alvi, Rajaa Hussein, Reem Al Swayeh, Saleh Al-Dgither, and Muhammad M Hammami, Determination of amlodipine in human plasma by liquid chromatography-electrospray ionization-tandem mass spectrometry: Application to pharmaco-kinetics and bioequivalence studies. Sixth "International Conference and Exhibition on Analytical and Bioanalytical Techniques". World Congress on Bioavailability & Bioequivalence Pharmaceutical (R&D) Summit, Valencia, Spain, September 01-03 2015.

FEE-FOR-SERVICE

- 12th Semiannual Liquid Chromatography: Concept And Hands-On Training Course SR12,000.

COMPARATIVE MEDICINE DEPARTMENT

COMPARATIVE MEDICINE

CHAIRMAN

Abdullah Assiri, DVM, PhD

ADMINISTRATIVE SUPPORT STAFF

Janalie Narral

Talal Alasmari

THE DEPARTMENT OF COMPARATIVE MEDICINE'S MISSION IS TO support research and patient care through the provision of high quality animal modeling programs. Our laboratory animal modeling and care programs comply with the established standards of the "Guide for the Care & Use of Laboratory Animals" in accordance with both national and international standards. The Department strives to produce novel, as well as to refine existing animal models while encouraging the use of alternatives to animal research. The department research activities are focusing on 2 main areas; infertility and organ transplant research.

In 2015, there is 15% increase in the number of projects that are supported by CMD. This year, the CMD hosted and/or co-organized surgical workshops and training programs in coordination with several hospital departments. A total of 566 participants including instructors, residents, and fellows were involved in these training activities, an increase of 65% from last year. The CMD hosted 184 future scientists, AlRazi, Mawhiba and AlFaisal University students, an increase of 67%, compared to 110 students in 2014.

The Laboratory Animal Services (LAS) at the Main Hospital and the KFNCCC provide specific pathogens free (SPF) laboratory animals to approved RAC projects. In 2015, the CMD-LAS has supported many research projects by providing 8,748 animals, an increase of 23% from last year.

Moreover, the CMD Histology and Clinical Pathology and Diagnostics Laboratories have continued to support various biological samples processing for research and/or biosecurity purposes. In 2015, over 3,320 biological samples were processed and analyzed which benefited many investigators and translated in 48% increase from last year. The CMD Genotyping Core Services genotyped 1,220 samples in 2015 for different transgenic and knockout animals.

These achievements were made possible by our staff's dedication, enthusiasm and determination and the tremendous support from The Research Centre Administration to make all our activities for this year a success.

SN	ACTIVITIES	TOTAL NO.
1	Number of Approved Research Projects and Training Programs that were supported by CMD	83
2	Number of Small and Large Animals that were provided by CMD Laboratory Animal Services for various training and research programs	8478
3	Number of Biological Samples that were processed by CMD Histology and Clinical Pathology & Diagnostic Laboratories	3320
4	Number of Small and Large Animals used in surgical research training	390
5	Number of Genotyping Assays that were performed by the CMD Genotyping Core Facility for different transgenic and knockout mice	1220
6	Number of Participants in surgical workshops and training programs that were hosted and/or co-organized by CMD in coordination with different hospital departments using various animal models	566
7	Number of Students from King Abdulaziz and His Companions Foundation for Giftedness and Creativity (Ibn Sena), Future Scientist and Al Faisal University that were trained at the CMD	184
8	Number of Publications that CMD staff authored/co-authored	18

WORKSHOPS & TRAININGS

1. Advanced Microsurgery "Hands-on" Course
2. Basic Surgical Skills
3. Basic Microsurgery course
4. Pediatric Flexible Bronchoscopy Course
5. Pediatric Laparoscopy Course
6. Minimal Invasive Surgery for the Esophagus
7. Tracheal and Lung Lobectomy Minimal Invasive Surgery
8. Advanced Gynecological Laparoscopy Training Course
9. Introduction on Using Laboratory Animals in Biomedical Research
10. Advanced Urological Laparoscopy Training Course
11. Alfaisal University Clerkship Program
12. Advances in Surgical Haemostasis Workshop
13. Future Scientist Program
14. Al Razi Program
15. Ibn Sena Program

PUBLICATIONS OF CMD STAFF

- IL-12 immunotherapy of BrafV600E-induced papillary thyroid cancer in a mouse model. Parhar RS, Zou M, Al-Mohanna FA, Baitei EY, Assiri AM, Meyer BF, Shi Y. *Lab Invest*. 2015 Oct 26. doi: 10.1038/labinvest.2015.126. [Epub ahead of print].
- TSH overcomes BrafV600E-induced senescence to promote tumor progression via downregulation of p53 expression in papillary thyroid cancer. Zou M1, Baitei EY1, Al-Rijjal RA, Parhar RS, Al-Mohanna FA, Kimura S, Pritchard C, Binessa HA, Alzahrani AS, Al-Khalaf HH, Hawwari A, Akhtar M, Assiri AM, Meyer BF, Shi Y. *Oncogene*. 2015 Oct 19. doi: 10.1038/onc.2015.253. [Epub ahead of print].
- KRASG12D-mediated oncogenic transformation of thyroid follicular cells requires long-term TSH stimulation and is regulated by SPRY1. Zou M1, Baitei EY1, Al-Rijjal RA, Parhar RS, Al-Mohanna FA, Kimura S, Pritchard C, BinEssa H, Alanazi AA, Alzahrani AS, Akhtar M, Assiri AM, Meyer BF, Shi Y, *Lab Invest*. 2015 Jul 6. doi: 10.1038/labinvest.2015.90. [Epub ahead of print].
- Role of DCAF17 in Spermatogenesis "A Knockout Mouse Model", a Potential Model for Globozoospermia. Abdullah Assiri, Asmaa Ali, Hala Ahmed, Bhavesh Mistry, and Fowzan Alkuraya, European School for Advanced Mouse Phenogenomics (Phenomin), *Château du Liebfrauenberg*, June 08-12, 2015, Alsace, France (Poster).
- LPS Ligation of TLR4 on Alveolar Macrophages Promotes PMN and CDR+ T Cell Transendothelial Migration. Saba Al Heialy, Abdul Ahad Shaikh, Abdullah Mohamed Assiri, Tau Rui, Moni Nader, and Peter Kvietys, Experimental Biology Meeting, March 28-April 1, 2015, Boston, USA (Poster).
- Control of histone H3 phosphorylation by CaMKIIδ in response to haemodynamic cardiac stress. Awad S, Al-Haffar KM, Marashly Q, Quijada P, Kunhi M, Al-Yacoub N, Wade FS, Mohammed SF, Al-Dayel F, Sutherland G, Assiri A, Sussman M, Bers D, Al-Habeeb W, Poizat C. *J Pathol*. 2015 Mar;235(4):606-18. doi: 10.1002/path.4489.
- Targeted complement inhibition and microvasculature in transplants: A therapeutic perspective. Khan MA, Hsu JL, Assiri AM, Broering DC. *Clin Exp Immunol*. 2015 Sep 25. doi: 10.1111/cei.12713. [Epub ahead of print].
- Complement mediators: key regulators of airway tissue remodeling in asthma. Khan MA, Assiri AM, Broering DC. *J Transl Med*. 2015 Aug 20;13:272. doi: 10.1186/s12967-015-0565-2.
- Complement and macrophage crosstalk during process of angiogenesis in tumor progression. Khan MA, Assiri AM, Broering DC, *J Biomed Sci*. 2015 Jul 22;22(1):58. doi: 10.1186/s12929-015-0151-1.

- Deletion of low molecular weight protein tyrosine phosphatase (Acp1) protects against stress-induced cardiomyopathy. Wade F, Quijada P, Al-Haffar KM, Awad SM, Kunhi M, Toko H, Marashly Q, Belhaj K, Zahid E, Al-Mohanna F, Stanford SM, Alvarez R, Liu Y, Colak D, Jordan MC, Roos KP, Assiri A, Al-Habeeb W, Sussman M, Bottini N, Poizat C. *J Pathol*. 2015 Jul 25. doi: 10.1002/path.4594.
- A Novel Rat Model of Liver Regeneration: Possible Role of Cytokine Induced Neutrophil Chemoattractant-1 in Augmented Liver Regeneration. Dipok Kumar Dhar, Goran Mohammad Hamid, Soumil Viyas, Dieter Clemens Broering, Massimo Malago. *Ann Surg Innov Res*. 2015 Nov 2;9:11.
- Anti-inflammatory pre-treatment to reduce mobilization-induced liver inflammation in mice: novel model to study liver injury.Hendrikx Tim Sverdlov R, Dipok Dhar, Mpabanzi L, Piersma, Céline, Olde Damink Steven. *Modern Research in Inflammation* (accepted). 24 Jul 2015
- Amyloid persistence in decellularized liver: biochemical and histo-pathological characterization. Mangione Patrizia, Mazza Giuseppe, Simons Paul, Al-Shawi Raya, Ellmerich Stephan, Taylor Graham, Gilbertson Janet, Dhar Dipok Kumar, Hawkins Philip, Pinzani Massimo, Bellotti Vittorio. *Amyloid* (accepted). 15 Oct 2015.
- Ultrasonic Hepatotripsy for Cell Therapy: A novel approach to treatment of inherited liver disorders. Presented as Senior author in International Society for Therapeutic Ultrasound held in April 2015 in Utrecht, the Netherlands. Dipok Dhar (Poster).
- Mohamed FE, Al-Jehani RM, Minogue SS, Andreola F, Winstanley A, Olde Damink SW, Habtesion A, Malagó M, Davies N, Luong TV, Dhillon AP, Mookerjee RP, Dhar DK*, Jalan R*. Effect of toll-like receptor 7 and 9 targeted therapy to prevent the development of hepatocellular carcinoma. *Liver Int*. 2015 Mar;35(3):1063-76.(*joint Senior Author)(UCL project).
- Giuseppe Mazza, Krista Rombouts, Andrew Hall, Luca Urbani, Tu Vinh Luong, Walid Al-Akkad, Lisa Longato, David Brown, Panayiotis Maghsoudlou, Amar P. Dhillon, Barry Fuller, Brian Davidson, Kevin Moore, Dipok Dhar, Paolo De Coppi, Massimo Malago, and Massimo Pinzani. Decellularized human liver as a natural 3D-scaffold for liver bioengineering and transpolantation. *Scientific Reports*. *Sci Rep*. 2015 Aug 7;5:13079.(UCL project).
- PLCz or PAWP: revisiting the putative mammalian sperm factor that triggers egg activation and embryogenesis. Junaid Kashir, Michail Nomikos, Karl Swann, and F. Anthony Lai, accepted on February 23, 2015.
- Functional disparity between human PAWP and PLCz in the generation of Ca21 oscillations for oocyte activation. MichailNomikos, Jessica R. Sanders, Junaid Kashir, Randa Sanusi, Luke Buntwal, Daniel Love, Peter Ashley, David Sanders, Paul Knaggs, Adnan Bunkheila, Karl Swann, and F. Anthony Lai, accepted on June 19, 2015.

KFSH&RC COLLABORATIONS

1. Department of Cyclotron and Radiopharmaceuticals
2. Department of Cell Biology
3. Department of Genetics
4. Department of Molecular Oncology
5. RC-KFNCCC
6. Cardiovascular Research Program
7. Molecular Biomedicine Program
8. Stem Cell and Tissue Re-engineering Program
9. Department of Neuroscience
10. Department of Orthopedics
11. Department of Pathology and Laboratory Medicine

12. Department of Pediatrics
13. Department of Surgery
14. Department of Urology
15. Heart Centre
16. Organ Transplant Centre

NATIONAL COLLABORATIONS

1. Security Forces Hospital
2. National Guard Hospital
3. National Commission for Wildlife Conservation and Development
4. King Abdulaziz City for Science and Technology
5. King Abdulaziz and his Companions Foundation for Giftedness and Creativity
6. King Saud University
7. King Fahad Medical City
8. King Abdullah International Medical Research Centre
9. King Faisal University
10. King Saud Medical City
11. King Abdulaziz University
12. University of Dammam
13. Ministry of Agriculture
14. Qassim University
15. King Khalid University

INTERNATIONAL COLLABORATIONS

1. The Fondazione Guido Bernardini (FGB)
2. NOXXON Pharma AG, Berlin Germany
3. Cynata therapeutics, Australia
4. Brunel University, UK
5. University College London, UK

LIST OF RAC ACTIVE PROJECTS

SN	RAC NO.	PROJECT DESCRIPTION
1	2022 007	Microsurgery Training
2	2022 008	Microsurgery Intensive Hands-On Course
3	2032 002	Training of Surgical Residents in Bowel Anastomosis
4	2050 032	The Effect of Alpha Adrenergic Blockers on the Ureter: An *In Vivo* Study in the Dog
5	2060 016	Investigating the Role of the Actin-Bundling Protein (Fascin) in Regulating Dendritic Cells Migration and Breast Cancel Metastasis in Saudi Population
6	2070 023	Genetics of Vision Loss in Saudi Arabia
7	2080 006	Genetics of Craniofacial Birth Defects in Saudi Arabia
8	2080 009	Investigation of the Role of Stromal Fibroblasts in the Development of Breast Carcinoma: The Tumor Suppressor $p16^{INK4A}$ Protein as Target
9	2080 019	Transcriptional Regulation of TCR α/δ Locus
10	2080 027	Study of the Anti-Cancer Properties of PAC (A Novel Curcumin Analogue) *In Vitro and In Vivo*
11	2080 029	Cyclooxygenases: Target for Epithelial Ovarian Cancer Prevention and Treatment
12	2080 031	Role of C-MET in Saudi Arabian Papillary Thyroid Carcinoma for Novel Therapy
13	2080 046	RoRγt Role in T Cell Development, Autoimmunity and Transformation
14	2080 051	Positional Cloning of Developmental Relevant Genes from Patients with Balanced Chromosomal Rearrangements
15	2080 052	Proteomic Analysis, Anti-Resorptive Properties and Tumor Cell Cytotoxicity of Osteodex in Bone Metastasis from Breast and Prostate Cancer
16	2090 014	Development of 18F-Labeled Radiopharmaceuticals Beyond $^{[18F]}$FDG for Use in Oncology and Neurosciences
17	2090 028	Role of Excitatory Amino Acids in Trans Fat-induced Obesity, Dyslipidemia, Hepatic Steatosis and Cognitive Impairment
18	2100 003	Radiolabeled Bioactive Peptides: Potential Molecular Targeting Radiopharmaceuticals for Cancer Imaging and Therapy
19	2100 006	Making and Characterization of the Mouse Model for Hypogonadism, Alopecia, Diabetes Mellitus, Mental Retardation and Extrapyramidal Syndrome

SN	RAC NO.	PROJECT DESCRIPTION
20	2100 013	The Anti-breast Cancer Potential of Eugenol
21	2100 016	Phenotypic Anchoring, Global Gene Expression Profiling and Correlative Clinical Outcomes During the Development and Progression of Diabetic
22	2100 018	Study the potential anti-cancer properties of camel's urine
23	2100 023	Role of LMPTP in Cardiovascular Diseases
24	2100 024	Epigenetic regulation by Nuclear Calcium in the Heart
25	2100 026	Role of Scaffold Protein Striatin in Regulating Cardiac Remodelling
26	2102 001	Annual Pediatric Flexible Bronchoscopy Course (Animal Training Program)
27	2110 002	Development of Ga-68 Based PET-Radiopharmaceuticals for Management of Cancer and Other Chronic Diseases
28	2110 011	The Use of Rat Embryonic Stem Cells in Decellilarized Rat Hearts
29	2110 013	Prolyl Hydroxylase Inhibitor Pretreatment in Cisplatin Induced Acute Kidney Injury Model
30	2110 021	Molecular Characterization of the Mechanisms in BRAF Splicing Variants and Pseudogene Mediated Signaling and Thyroid Tumorigenesis in Transgenic Mice
31	2110 025	Anti-Tumor Activity of XIAP Inhibitor Embelin on Mice Xenografts of Epithelial Carcinomas
32	2110 032	The miR29a-TTP axis regulation of RNA binding protein, HuR, and CXCR-4 in invasive breast cancer
33	2110 034	Development of New Sutureless Microsurgery Device for Anastomosis of Small Blood Vessels
34	2111 101	Expression of CYP24, the catabolizing enzyme of Vitamin D, in thyroid tumor development and progression
35	2112 002	Microsurgery Training
36	2112 003	Microsurgical Practice for Residents
37	2120 002	Research and Development of Lutetium - 177 based Radiopharmaceuticals for Targeted Radionuclide therapy of Cancer
38	2120 005	Duodenal Tubular Flap in the Surgical Repair of Choledochal Cyst
39	2120 006	Bio-screening of Herbs Liquids used in the kingdom for Anti-cancer Activity: Implications in Discovery of Anti-Cancer Agents
40	2120 015	Establishment of a Living Donor Liver Transplantation Model in Baboons (Pilot Study)
41	2120 016	Development and Optimization of Zirconium-89 Production and Clinical TF-PET/CT Imaging Protocols for Breast Tumor and Immunotherapy Planning
42	2120 019	Pharmacokinetics of Different Doses of Caffeine Mixed in Infant Formula: An Animal Pilot Study
43	2120 034	Study the Potential Role of IL-6 in the Cross –Talk between Carcinomas and their Stromal Fibroblasts
44	2130 004	In the hand, can the flexor tendon heal to the volar plate?
45	2130 007	IL-12 Gene Therapy of Thyroid Cancer in $BRAF^{V600E}$ Transgenic Mouse Model
46	2130 008	Characterization of Lacrimal & Ocular Mucosal Immunity in the Arabian Camel (Camelus Dromedarius): Implications for the Management of Sjoegren's Syndrome
47	2130 011	Interactive Effects of Neonatal Exposure to Excitatory Amino Acids on Normal Metabolism, Learning & Memory: Role of N-methyl-D-aspartate receptors
48	2130 017	Characterization of Fascin Role in Stem Cell Function Knockout Mouse Model
49	2130 022	{18F} Radiopharmaceuticals / Radiotracers as Positron Emission Tomography Imaging Tools-Beyond {18F}-2-fluoro 2-deoxy glucose {18f} FDG
50	2130 023	Experimental Study to Identify Early Stroke Biomarkers
51	2130 038	Potential Role of Glutamate as an Immunoregulator: Effects on Neutrophil Function
52	2130 040	Preclinical *In Vitro* and *In Vivo* Anti-Tumor Evaluation of Small Molecule Inhibitors of Cancer Stem Cells
53	2132 001	3rd International Difficult Airway Management Workshop
54	2132 002	Single Incision Laparoscopic Surgery (SILS) Training
55	2132 003	Establishing Heterotopic Heart Transplant in a Rat Model

SN	RAC NO.	PROJECT DESCRIPTION
56	2132 004	Advanced Urological Laparoscopy "Hands-on" Course
57	2140 001	The Role of the Immunomodulatory Molecule B7-H1 (PD-L1) in the Initiation and Maintenance of Cancer Stem Cells
58	2140 003	Cellular and Molecular Profiling of Primitive HSC Subsets in Umbilical Cord Blood & Bone Marrow Samples: Implications for Cell Therapy
59	2140 011	Role of T Cells in LPS-Induced Lung Inflammation and Dysfunction
60	2140 015	CaMKII Epigenetic Signaling in Heart Disease
61	2140 017	Unravelling the Molecular Link Between Obesity Breast Cancer: Role of Adipocytes & $P16^{INK4A}$
62	2140 023	Investigation of Sprouty Family of Proteins in Thyroid Cancer Development and Progression
63	2140 031	Preventive and Therapeutic Potential of PAC on Thyroid Cancer
64	2140 035	Role of Epoxyeicosatrienoic Acids in Liver Regeneration
65	2140 036	Role of Regulatory Cells (TREGS) in Inducing Immune Tolerance in Mouse Model of Trachea Transplantation
66	2141 005	Rescue Therapy of Retrieved Organs from Deceased Donors: Liver *Ex Vivo* Machine Perfusion
67	2141 037	Elucidate the Mechanisms through which Febrile-Range-Hyperthermia primes Neutrophils for Chemokine-Directed Trans-Vascular Egress
68	2141 055	Rescue Therapy of Retrieved Organs from Deceased Donors: Liver *Ex Vivo* Machine Perfusion
69	2142 001	Rapid, Simplified Training Technique for Heterotopic Cervical Heart Transplantation in Mice and Rat
70	2142 002	Advances in Surgical Haemostasis Workshop
71	2142 003	Minimal Invasive Training for Pediatric Surgery
72	2150 002	Role of CDKN2A (Ink4a/ARF) in Regulating KrasG12D Mediated Oncogenic Transformation of Thyroid Follicular Cells
73	2150 006	Role of AUF1 in Controlling VE6F-A and the Angiogenesis in Osteosarcomas: Potential Prognostic/Predictive Marker
74	2150 007	Role of Striatin in Regulating Calcium Homeostasis in Cardiomyocytes: a Novel Regulator of the L-Type Calcium Channel
75	2150 012	Liver Tissue Engineering and Liver Transplantation
76	2150 016	Studying the *In Vivo* Side Effects of Dexamethasone at Metabolic Level
77	2150 017	Role of Complement Factor C5A and Surfactant Protein-D in Preserving Microvasculature in Rejecting Allografts
78	2150 019	Heterotopic Xenotransplantation of Transgenic Mouse Heart Expressing the Vacinia Virus Complement Control Protein in Concordant and Discordant Species
79	2150 029	Role of LMPTP in Atherosclerosis and Ischemic Heart Disease
80	2150 030	Development of Mice Genetic Engineering and Assisted Reproductive Technologies (MGEART)
81	2152 001	Animal Workshop on Tracheal & Esophageal Surgeries
82	2152 002	Hemostatic Agents in Surgery
83	2152 003	Training Workshops on Different Surgical & Laparoscopic Techniques

LABORATORY ANIMAL SERVICES

HEAD

Falah Almohanna, DVM, MSc

KFSH&RC STAFF

Rolando Monzaga
Pio Oliveras
Saad Aldurgham
Alberto Capuno
Bahaa Salem
Merfat Elyan

KFNCCC&R STAFF

Ruben Delos Santos
Wilfredo Antiquera
Baltazar Caducio
Mona Saleh

THE LAS MAINTAINS QUALITY LABORATORY ANIMALS AND PROVIDES associated technologies for basic and translational research that is undertaken by scientists and physicians. The LAS maintains animal well-being and ensures that prudent, ethical and scientific use of animals is in accordance with both national and international guidelines. The LAS staff is committed to implement CMD health and biosecurity program which is integral component of providing quality services.

Animal technician changing cages.

Animal technician changing the animals.

EXPERIMENTAL SURGERY AND DIAGNOSTIC IMAGING SECTION

HEAD

Ra'afat Elsayed, DVM, MVSc

STAFF

Farraj Alsamer

Abdulrahman Alzuhaifi, MSc

Ludivina Apilado, RN

Sahar Salem, RN

STATE-OF-THE-ART EXPERIMENTAL SURGICAL FACILITIES THAT ARE designed to perform acute, survival procedures and cadaver dissections for research and training purposes. The section provides a unique opportunity for surgeons and researchers to develop and refine surgical skills and to explore new innovations. The section consists of veterinary anesthetists, perfusionist, surgeons and nurses. This year, the section has added 2 additional rodent surgical procedure rooms to meet increasing demand.

CMD Operating Room Theater.

Microsurgery Course.

Surgery Workshop.

COMPARATIVE PATHOLOGY AND DIAGNOSTIC LABORATORY

HEAD

Abdullah Assiri, DVM, PhD

STAFF

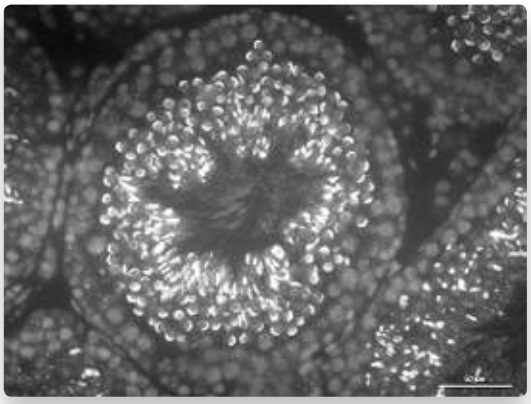
Asmaa Ali, DVM

Hala Ahmed

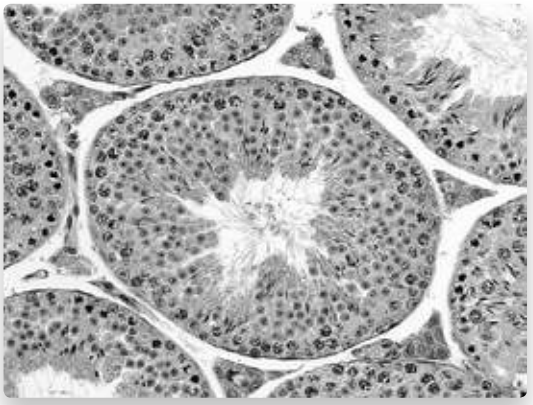
THE SECTION AIDS INVESTIGATORS TO CHARACTERIZE PATHOLOGICAL progress of natural and/or induced diseases in animal models. This section offers complete animal health screening, histopathology, clinical pathology and diagnostic services for laboratory animals that are used in biomedical research and training at KFSH&RC. The section play important role on implementing KFSH&RC animal care program biosecurity and environmental screening.

Embedding machine.

Automated Complete Blood Count (CBC) Picture Machine.



DAPI Immunofluorescent for seminiferous tubules of adult mice.



H&E Staining for seminiferous tubules of adult mice.

COMPARATIVE FUNCTIONAL GENOMICS

HEAD

Abdullah Assiri, DVM, PhD

STAFF

Bhavesh Mistry, MSc, PhD

Mohammed Rajab

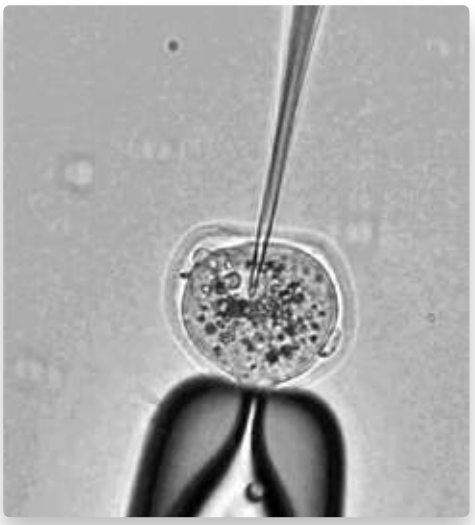
Razan Abdullah

Maha Alanazi

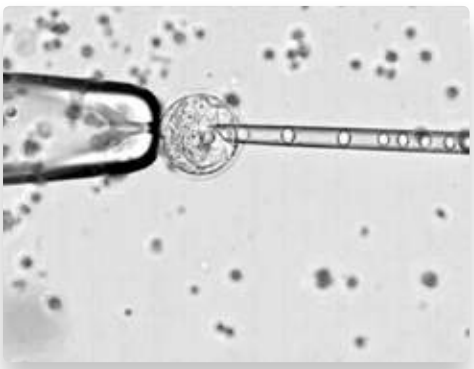
THE SECTION STRIVE TO CHARACTERIZE NATURAL AND/OR INDUCED animal models of physiological relevancy for important health problems such as infertility, endocrine disrupters, cancer, genetics, cardiovascular diseases and diabetes. The section provides various phenomic and genomic tools to investigate existing and emerging model organisms to address unique Saudi population diseases. We are currently working to investigate role of DDB1-CULL4A Associated Factor 17 (DCAF17) in spermatogenesis as potential mouse model for human azoospermia. In addition, the section is developing mouse genetic engineering to produce novel animal models for human diseases and assisted reproductive technologies for colony health, management and biobanking.

Pronuclear injecting technology (PNI) microinjection of mouse embryos.

Collection of mouse embryos.

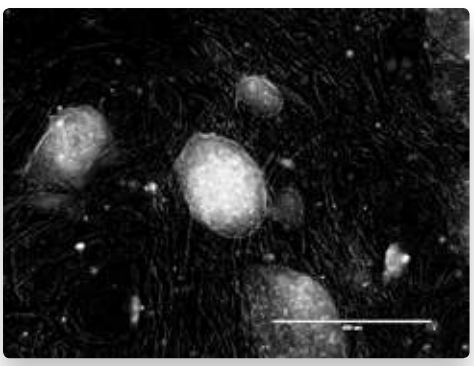


400x magnification Pronuclear Injecting Technology (PNI) under microscope.



200x magnification Mouse Embryonic Stem Cells (MESC) Injection

Diff-quick stain for epididymal sperm from C57BL mice.



Mice embryonic stem cells (MESC) expressing transgenic red fluorescence protein.

ORGAN TRANSPLANT RESEARCH SECTION

HEAD

Prof. Dieter Broering, MD, PhD, MBA, FEBS

STAFF

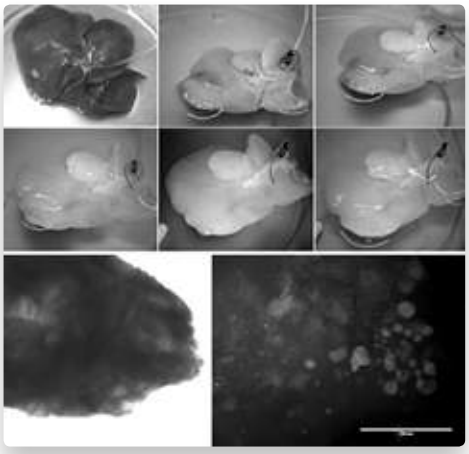
Dipok Dhar, MBBS, PhD

Mohammad Khan, MSc, PhD

Fatimah Alanazi

Abdullah Altuhami

THE ORGAN TRANSPLANT RESEARCH SECTION WAS ESTABLISHED to provide basic transplantation research using molecular, cellular and animal models including non-human primates, and to extrapolate basic research findings into translational research with clinical applications. Ongoing projects including novel concepts of liver regeneration, tissue engineering, organ transplant immunological modulation and organ re-conditioning will develop innovative treatment modalities for patients with terminal organ failure.



Liver Scaffold Decellularization.

Machine used for Liver Scaffold Decellularization.

Using Flow Cytometer for Cell Analysis.

CYCLOTRON AND RADIOPHARMACEUTICALS DEPARTMENT

CYCLOTRON AND RADIOPHARMACEUTICALS

ACTING CHAIRMAN
Ibrahim Al-Jammaz, PhD, FRSC

ADMINISTRATIVE SUPPORT STAFF
Jhonna L. Canicosa
Nora B. D'Souza

CYCLOTRON AND RADIOPHARMACEUTICALS (C&R) DEPARTMENT performs two distinct functions in the Research Center: Radiopharmaceuticals manufacturing; and Radiotracer Research.

Radiopharmaceutical manufacturing: Radiopharmaceuticals are the pharmaceutical products that are labeled with radioactive isotopes, and are the key ingredients in practice of nuclear medicine, either for diagnostic imaging or for therapy. C&R Department is the only facility of this kind within the geographical region manufacturing these specialty products.

Working towards the ultimate goal of comprehensive manufacturing facility, several new products are added at regular intervals. As a result, some 45 nuclear medicine centers in the Kingdom and abroad rely upon products manufactured in the C&R production facility. An obvious requirement for pharmaceutical manufacturing is the adherence to the national and international guidelines of Good Manufacturing Practices (GMP). C&R Department manufacturing protocols are not only designed to adhere to the regulatory requirements but also follow the ISO 9001:2015 Quality Management System for further quality enhancement.

Radiotracer Research: Radiotracers are the tools for probing at molecular level the biochemical and physiological processes. A well designed molecule labeled with an appropriate radioisotope has the potential to probe specific biological systems *in vivo* with minimum perturbation of the whole organism. Research Section staff in the C&R Department engages in research and development with an aim to develop radiotracers through hypothesis driven research that entails developing radiolabeling procedures culminating into bioactive molecules tagged with radioisotopes.

Year 2015 has indeed become a landmark year for C&R Department. The production and research team has developed protocols for manufacturing additional PET radiotracers for routine use, improving potential for advanced and specific diagnostic medical imaging performed at nuclear medicine centers within the Kingdom.

On the research and development front, achievements included not only the customary extramural research grant funds and large number of international publications and presentations, but also the production and quality assurance protocols for new radiotracers, and indigenously fabricated complex devices for manufacturing radioisotopes and radiopharmaceuticals. The exceptional R&D efforts are ultimately leading towards ever more comprehensive radioisotope and radiopharmaceuticals manufacturing within the C&R Department and also resulting in significant cost saving for the Hospital

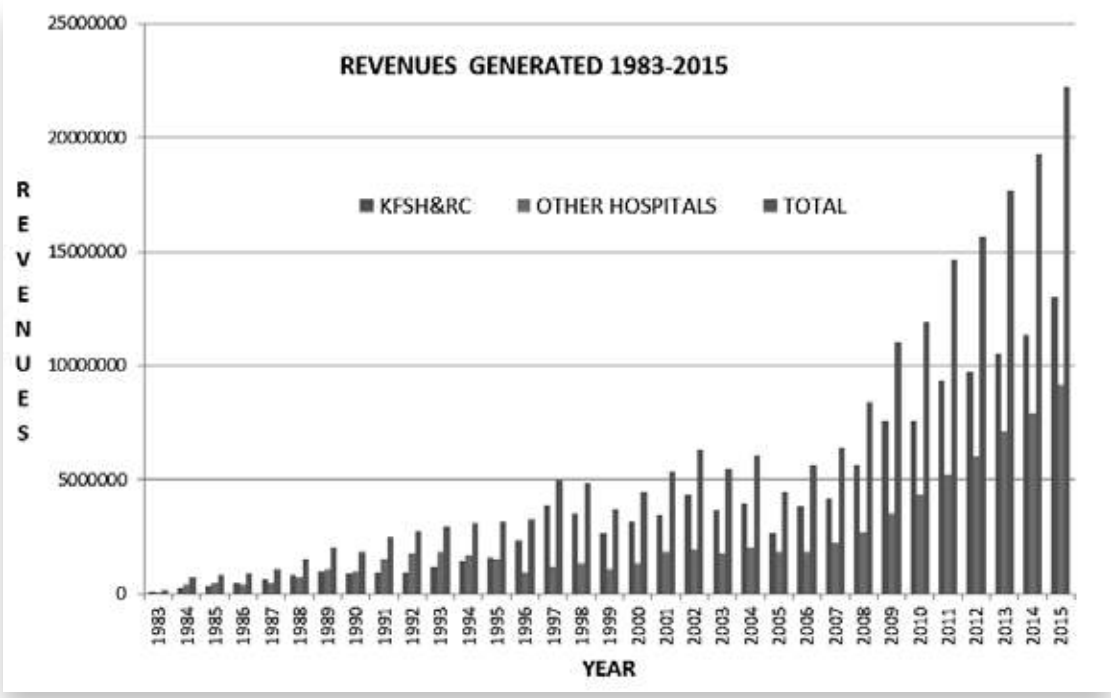
MAJOR ACHIEVEMENTS IN YEAR 2015

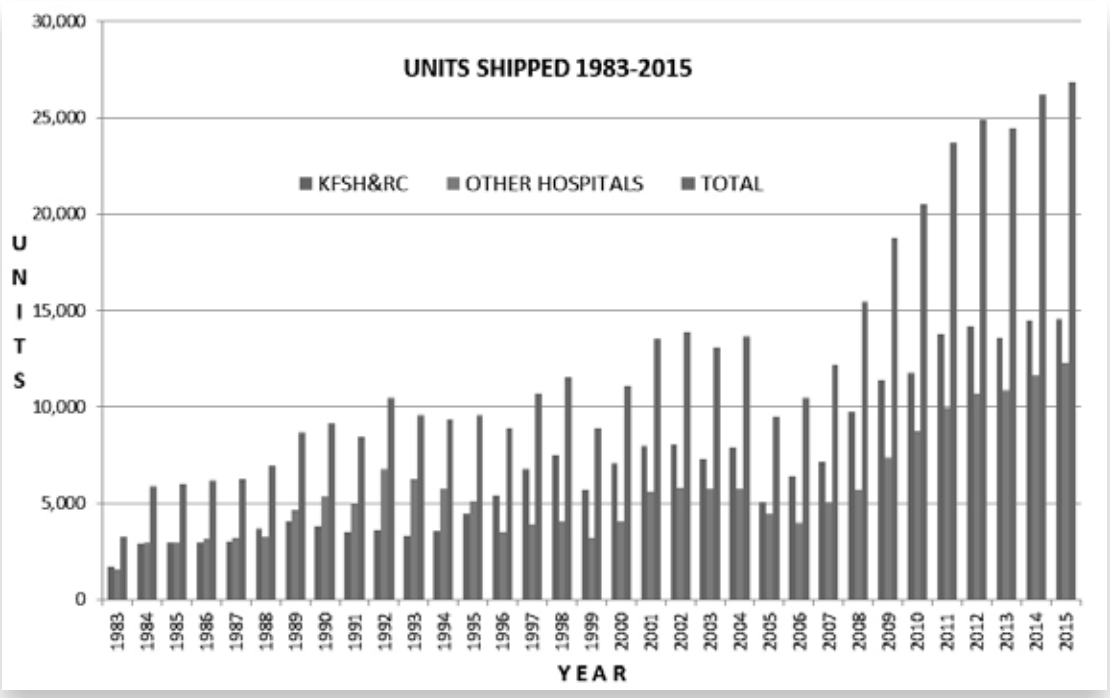
Collective effort of the C&RD staff has resulted in significant achievements as noted in the following:

- New radiopharmaceutical product developed and being routinely delivered to Nuclear Medicine (F-18 Choline); new radiopharmaceuticals product developed and validated (F-18 DOPAMINE).
- The system was developed to automatically control the F-18 Fluoride distribution among the FDG synthesizers. This system has been successfully installed and minimizes the human error when manually selecting different modules. It reduces the exposure of C&R operator/staff from radiation; it has also increased the activity produced by applying auto system valves.
- A new RF system was installed on the CS30 aiming to improve the performance of operation. The old system had major drawback by having a wood based support. The latter was giving continuous problems and in many cases wood burns. Following from installation of the new aluminum based RF System; performance of CS30 Cyclotron has increased by at least 25%.
- Upgrade of molecular imaging group by introducing Nano PET/CT imaging modality.
- Development of Computerized System for preparation of Production Batch Records and Quality Control (QC) forms for routine radiopharmaceuticals production.
- Development of Online Customer Satisfaction Survey; enabling us to maximize customer input and utilize sophisticated data analysis.
- Incorporation of Automated Dispensing System for F-18 FDG Injection carrying out the y operation based on GMP (Good Manufacturing Practices); operation of FDG Dispensing System results in accurate amount of FDG shipped to outside customer, and enhanced radiation safety for the operators.
- Achieving the Quality Management System objectives of radioisotopes production: radiopharmaceuticals distribution of 1,379 numbers of batches produced; satisfying customer requirement of products shipping:97.3% Process success rate:99.4%

and Conformity of radiopharmaceuticals to specifications:99.6%.

- Extramural research grants funding to the tune of SR ~10 million with twelve (12) on-going and new research projects.
- Six (6) publications in peer reviewed international journals and eighteen (18) abstract presentations at international conferences.
- International Best Abstract Award from American Society of Nuclear Medicine (ASNM) received by C&RD staff in Baltimore, MD, USA on 07 June 2015.
- Successful production and distribution of 26,855 unit doses; generating revenues of 22,212,952 Saudi Riyals from January to December 2015.
- We have maintained our ISO 9001-QMS certification.
- Two of our publications were selected among the top abstracts at the Annual Meeting of Society of Nuclear Medicine held in Baltimore, Maryland, USA, June 2015.
    a. I. Al Jammaz, B. Al-Otaibi and S. Okarvi, Synthesis of novel 18F [FDG] labeled rhodamine: A potential PET myocardial perfusion imaging agent, SNMMI, Baltimor, June, 2015.
    b. S. Okarvi and I. Al Jammaz, Synthesis and preliminary evaluation of a rhodamine-angiotensin conjugate as a breast tumor imaging agent, SNMMI, Baltimore, June, 2015.
- Participate in the Training and Education activities namely:
    a. Al-Razi Program for under Graduates students (July-August, 2015).
    b. Supervising MSc student- Abdulrahman Al-Omar, PhD student from King Saud University, College of Science, Chemistry Department, Project title "Synthesis and characterization of new copper complexes as potential radiopharmaceuticals"





RESEARCH PROJECTS

PROJECT TITLE: Radiolabeled Bioactive Peptides: Potential Molecular Targeting Radiopharmaceuticals for Cancer Imaging and Therapy
KACST supported project # AT-30-231 (SR 2,196,000).

INVESTIGATORS: *I. AlJammaz (PI) and S. Okarvi*

PROJECT TITLE: Production and Utilization of Positron Emitters Copper-64 and Iodine-124 for Medical Applications
IAEA supported project # 15946 (SR 67,000)

INVESTIGATORS: *F. Al-Rumayan (PI) and I. AlJammaz (Co-PI)*

PROJECT TITLE: Development of Ga-68 based PET-Radiopharmaceuticals for Management of Cancer and other Chronic Diseases
IAEA supported project # 16424 (SR 67,000)

INVESTIGATORS: *I. AlJammaz, (PI), S. Okarvi (Co-I), A. Al-Rabiah (Co-I) and B Al-Otaibi (Co-I)*

PROJECT TITLE: Development of Y-90 and Lu-177 based Radiopharmaceuticals for Cancer Therapy
IAEA supported project # 16424 (SR 67,000)

INVESTIGATORS: *S. Okarvi, (PI) and I. AlJammaz (Co-I).*

PROJECT TITLE: Multimodality Imaging and Diagnosis of Chronic Respiratory Diseases Using Bone Marrow Derived Macrophages.
KACST supported project # NPST 10 (SR 1,844,500).

INVESTIGATOR: *I. AlJammaz (Co-PI)*

PROJECT TITLE: National Production of Zirconium-89 for Tumour Imaging and Immunotherapy Planning
KACST supported project # NPST 2120016 (SR 1,609,000)

INVESTIGATORS: *I. AlJammaz (Co-PI) and S. Al-Yanbawi (Co-I)*

PROJECT TITLE: Radiolabeling and Preliminary Evaluation of Laminin-1 Derived Peptide Antagonist that Blocks Angiogenesis and Tumor Growth
KACST supported project # ARP-29-15 (SR 865,200)

INVESTIGATOR: *M. Al-Qahtani (PI)*

PROJECT TITLE: [^{18}F]Radiopharmaceuticals/Radiotracers as Positron Emission Tomography imaging tools - Beyond [^{18}F]-2-fluoro 2-deoxy glucose ([^{18}F]FDG)
RAC# 2130 022 (SR 219,360)

INVESTIGATORS: *M. Al-Qahtani (PI) and F. Al-Rumayan (Co-PI)*

PROJECT TITLE: Remotely-Controlled Ammonia N-13 Target System for Cyclone-30 at KFSH&RC
RAC# 2130 030 (SR 256,000)

INVESTIGATORS: *F. Al-Rumayan (PI) and M. Al-Qahtani (Co-I)*

PROJECT TITLE: Intra-Operative Proton Radiotherapy (IOpTR), NCPT
RAC# 2120026, (SR, 1,950,000)

INVESTIGATOR: *F. Al-Rumayan (Co-PI)*

PROJECT TITLE: Accelerator-based Alternatives to Non-HEU Production of Mo-99/Tc-99m
IAEA supported project # 16424 (SR 67,000)

INVESTIGATORS: *I. AlJammaz (PI), F. Al-Rumayan (Co-I) and S. Al-Yanbawi (Co-I)*

PROJECT TITLE: Development of Krypton-81 Target system for Cyclone-30
RAC# 2100021, (SR, 70,000)

INVESTIGATORS: *F. Al-Rumayan (PI), I. AlJammaz (CO-PI), S. Yanbawi (Co-I), J. Schneider (Co-I) and Q. Akkam (Co-I)*

TOTAL FUND= 9,278,060.00

DEPARTMENT OF GENETICS

DEPARTMENT OF GENETICS

CHAIRMAN

Brian Meyer, PhD

ADMINISTRATIVE SUPPORT STAFF

Ralyn Alma O. Castillo

Maritess Santiago

Lilia Fernandez

Randa Al-Haj

DURING 2015 THE DEPARTMENT OF GENETICS REAFFIRMED ITS role as a leader in the field of inherited diseases, certainly those affecting the Arab world. Its participation in the Saudi Human Genome Program enabled investigation of all inherited diseases (the Mendeliome) in a large cohort of Saudi patients. This resulted in landmark publications covering known and novel inherited disorders in many disciplines of medicine.

ACADEMIC ACHIEVEMENTS OF 2015 INCLUDE

1. Characterization of over 2500 patients with Mendelian disorders. Highly accessed publication with a definitive approach for diagnosis of Mendelian Diseases.
2. Characterization of the molecular basis of Primary immune deficiency in KSA
3. Over 60 high quality publications related to hereditary disease and disease susceptibility
4. Departmental scientists are engaged in more than 20 externally funded research grants totaling in excess of SAR 40 million.
5. Identification of LACC1 as important gene in the biology of inflammatory syndromes such Rheumatoid Arthritis and Crohn's disease.
6. Expansion of the clinical, allelic, and locus heterogeneity of retinal dystrophies.
7. Deciphering the molecular genetic basis of Limb Girdle Muscular Dystrophy in Saudi patients.
8. Identification of the role of TSH in progression of Papillary Thyroid Cancer.
9. Genetic characterization of Parkinsons Disease in Saudi Arabia
10. Members serve on multiple editorial boards
11. Members act as reviewers for more than 10 scientific journals
12. Multiple International, National and intra-hospital collaborative research projects covering almost all areas of clinical medicine.

Successful research conducted in the department has also been reflected in members serving on editorial boards, acting as reviewers for prestigious journals and engaging in multiple national, regional and international collaborative research projects covering most disciplines of clinical medicine. Translation of research activities into screening and diagnostic services and provision of the most current genomic technologies to researchers are features of the department.

ALZHEIMER'S PROJECT

HEAD
Fadia El Bitar, PhD

MEMBERS
Sara Abdulaziz, BSc
Nada Majrashi, BSc
Maznah Al-Anazi, BSc
Hesa Al-Mutairi, BSc

ALZHEIMER'S PROJECT THAT HAS BEEN INITIATED RECENTLY AT the Department of Genetics is focusing on the following objectives:

1. Defining the genetic basis of Alzheimer's disease in Saudi Arabian Population by identifying known and novel genes causing the disease.
2. Modeling of the disease *in vitro* from Alzheimer's patients by direct conversion technology.
3. Discovery of neuroprotective drug(s) against proteins causing Alzheimer's disease.
4. Personalizing the Alzheimer's research by testing the *in vitro* response of each Alzheimer's patient to the newly identified neuroprotective drug(s).

Our research on Alzheimer's disease includes until now the Alzheimer's cases within King Faisal Specialist Hospital and Research Center in Riyadh and Jeddah, in addition to Dr. Suliaman Al Habib Medical Center in Riyadh.

RESEARCH PROJECTS

PROJECT TITLE: Genetics of Alzheimer's Disease and its Modeling in the Saudi Population
RAC #: 2120 020
Source of Funding: NSTIP funded project. Project code: 13 MED684-20

PRINCIPAL INVESTIGATOR: *Fadia El Bitar*
CO-INVESTIGATORS: *Nada Al-Tassan, Najeeb Qadi, Futwan Al-Mohanna, Saad Al Rajeh*

PROJECT DESCRIPTION: The major aims of this study are to define the molecular background of Alzheimer's disease (AD) in the Saudi Arabian population and to establish the modeling of Saudi Familial AD by direct conversion of fibroblast into functional neurons.

PROGRESS: Alzheimer's disease (AD) is a complex neurodegenerative disease that causes a progressive mental deterioration. Although AD is mainly sporadic occurs in the elderly, a minority of cases displays early onset familial AD (EO-FAD) that is related to genetic predisposition. Despite the progression in understanding the molecular basis of the disease in various populations, still the genetic component need to be investigated for Saudi patients. In the present work, we examined the genetic cause of AD in Saudi population. We recruited 91 sporadic and familial Saudi patients with full informed consent. All patients were reviewed by the Neuroscience clinics at KFSH&RC and at Dr. Suliaman Al Habib Medical Center with full clinical and family histories recorded. Genomic DNA was extracted from whole blood, quantified using standard methods and screened for mutations in the genes PSEN1, PSEN2, APP, APOEe4, SORL1 and other AD-related genes using direct sequencing. 85 novel sequence variants were detected in our samples, 60 were non-coding and 25 were exonic substitutions. Out of the 25 exonic substitutions, four were non-synonymous and 20 were synonymous substitutions. Two of the four non-synonymous substitutions were identified as potentially pathogenic mutations in SORL1 gene.

One of the main objectives in this study is to establish the modeling of Saudi familial AD by direct conversion of fibroblast into neurons. We followed a new approach in converting fibroblasts into neurons by a cocktail of chemical molecules that are known in the literature for their role in neurogenesis. We succeeded in obtaining neurons by establishing our cocktail of five molecules and the obtained neurons were positive for neuronal marker of immature neurons and were only viable until day 6 of culture.

SUBMITTED PROJECT

PROJECT TITLE: Potential Neuroprotective and Neurotrophic Candidates against the Toxicity of Beta-Amyloid Peptides Causing Alzheimer's Disease
Project # 2160 001
Submitted to ORA on December2015

PROJECT DESCRIPTION: This study will provide new understanding into the activities and the mechanism(s) of potential neuroprotective candidates that could be promising in therapeutic related to Alzheimer's disease.

PUBLICATIONS

ORIGINAL PEER REVIEWED FULL LENGTH PAPER

- Fadia El Bitar, Johann Meunier, Vanessa Villard, Marion Alméras, Kathiresan Krishnan, Douglas F. Covey, Tangui Maurice, Yvette Akwa (2014). Neuroprotection by the synthetic enantiomers of the neurosteroid PREGS and DHEAS against Abeta25-35 peptide-Induced toxicity in vitro

and in vivo in mice. *Psychopharmacology* 231(17):3293-312.

ABSTRACTS AND SCIENTIFIC CONFERENCE PROCEEDINGS

- Fadia El Bitar, Nada Al-Tassan, Najeeb Qadi, Saad Al Rajeh, Hatem Murad, Sara Abdulaziz, Nada Majrashi, Maznah Al Enizi, Amna Majrashi, Maha Al Turki, Samah Qassim (2015). Alzheimer's Disease in Saudi Patients: Molecular and Cellular Study (RAC#2120020). 2014 KFSH&RC Annual Research Report.15–16 April 2015.
- Fadia El Bitar, Nada Al-Tassan, Najeeb Qadi, Saad Al Rajeh, Sara Abdulaziz, Nada Majrashi, Maznah Al Enizi, Amna Majrashi, Maha Al Turki, Samah Qassim (2014). Molecular and Cellular Research on Alzheimer's Disease in Saudi Population (RAC#2120020). 2nd International Alzheimer's Disease Conference 2014. 24–26 November 2014. King Abdulaziz City for Science and Technology.
- Fadia El Bitar, Nada Al Tassan, Najeeb Qadi, Hatem Murad, Saad Al Rajeh, Amena Majrashi, Maha Al Turki, Sara Abdulaziz, Samah Qassim (2014). Recent Advances in Alzheimer's Research: Genetics of Alzheimer's disease and its Modeling in Saudi population (RAC#2120020). 2013 KFSH&RC Annual Research Report.16–17 April 2014.
- Tangui Maurice, Yvette Akwa, Fadia El Bitar, Johann Meunier, Vanessa Villard, Marion Almeras, Katherisan Krishnan, Douglas Covey. Neuroprotection by the Synthetic Enantiomers of the Neurosteroids PREGS and DHEAS against Beta-Amyloid 25-35 Peptide–Induced Toxicity (2013). Alzheimer and Dementia, Vol 9, Issue 4, Supplement page P507. Alzheimer's Association International Conference. Boston, USA. 12–18 July 2013.

FUTURE RESEARCH DIRECTION

Alzheimer's project will enlarge the scale of patient's enrolment from various parts of the Kingdom of Saudi Arabia in order to provide molecular and cellular data bases for Saudi Alzheimer's patients. In addition, working on developing an *in vitro* disease modeling and drug discovery will be for the benefits of the patients and the health system.

PUBLIC AWARENESS

Alzheimer's project is supported by Saudi Alzheimer's Association. As active members of Saudi Alzheimer's Association, Fadia El Bitar, PhD as PI (Principal Invesigator) and Najeeb Qadi, MD as COI (Co-investigator) of the project are focused on aspects of Alzheimer's awareness that deal with improving public access to information on our research and scientific approaches that are oriented to Saudi patients.

BEHAVIORAL GENETICS RESEARCH UNIT

HEAD

Nada Al Tassan, PhD

MEMBERS

Bashayer Al Mubarak, PhD
Jameela Shinwari, Msc
Amna AlMagrashi, BSc
Asma Tahir, BSc
Aisha Omar, BSc
Basma Al Tawil, BSc
Dania Khalil, BSc
Maha Al Turki, BSc
Eman Al-Yemni, BSc
Bahsair Safar, BSc
Sarh Bingahdir BSc
Msc Students:
Faten Al Naemi
Loulia Akras
Fahdah Aldahsh

THE OVERALL AIM OF THE UNIT IS TO EXPLORE THE MOLECULAR basis of complex disorders by studying multiplex families, where trait segregates, as well as sporadic single cases. Our research interests span many disease themes, including neurodegeneration, neurodevelopment, eye and reproductive system disorders.

In our laboratory we combine a variety of conventional and cutting edge approaches such as homozygosity mapping, candidate gene screening and next generation sequencing to identify novel causative and predisposing genes/mutations. Beyond genetic screening, we dedicate our efforts to functionally characterize the identified mutations in the relevant in vitro systems in order to understand the disease mechanisms. The ultimate goal of our research is contribute to the improvement of clinical diagnosis, genetic testing and counseling for affected individuals and families in Saudi Arabia.

RESEARCH PROJECTS

PROJECT TITLE: The Molecular Basis of Inherited Reproductive Disorders
RAC# 2091054

INVESTIGATORS: *Al Tassan N, Meyer B, Alkuraya F, Wakil S, Monies D, Crowley W*

PROJECT DESCRIPTION: This approved study in collaboration with Reproductive Endocrine Unit, Massachusetts General Hospital, Boston, USA, aims to identify genes that control puberty and reproduction in humans and characterize the phenotypic spectrum of patients with these genetic defects.

PROJECT PROGRESS: The sequencing of 1200 patients for 16 genes was completed; a number of novel and previously reported mutations were identified. Functional assessment of mutations is ongoing. The effect of digeneic mutation was ascertained in zebra fish. Selected samples were used to validate a specific gene panel covering the common gene involved in this disorder.

PROJECT TITLE: Genetic evaluation of Congenital Eyelid and Eye Movement Abnormalities
RAC# 2080020

INVESTIGATORS: *Khan A, AL-Tassan N.*

PROJECT DESCRIPTION: The objective of the study is to identify patients and families with congenital eyelid and eye movement abnormalities in order to screen for mutations in the common known genes (KIF21a, PHOX2a, ROBO3, HOXA1) and mapping to find causative genes in families with different rare forms of eyelid movement abnormalities.

PROJECT PROGRESS: Comprehensive screening for the whole open reading frame (ORF) of the previously reported common causative genes was completed. Mutations were identified and published. Two novel genes were identified in two families using exome sequencing; functional characterization was completed for mutations in on gene (data published in *AJHG* 2015). Functional assessment for the second gene is ongoing.

PROJECT TITLE: Characterizing Genetic Abnormalities in Autistic Spectrum Disorder (ASD) Patients in Saudi Arabia
RAC# 2080001

INVESTIGATORS: *AL-Tassan N, Aldosari M, Nester M, Meyer B, Bakheet D, Ayadhi L*

PROJECT DESCRIPTION: This multidisciplinary multicentre study aims to investigate the genetic basis of ASD patients in Saudi Arabia.

PROJECT PROGRESS: Linkage analysis identified several regions on different chromosomes; homozygosity confirmed these regions. Trio's analysis using NGS exome sequencing identified a number of potential disease causing *de novo*, autosomal dominant and autosomal recessive variants. All potential pathogenic variants were validated.

PROJECT TITLE: Functional and Molecular Characterization of Retinoblastoma in the Saudi Population.
RAC# 20130039

PROJECT DESCRIPTION: This is a collaborative project t with KKESH that aims to molecular profile RB tumors.

PROJECT PROGRESS: RB gene was screened for mutations in all samples available, targeted sequencing will be used to profile somatic mutation sin genes involved in different cancer related pathways.

KACST FUNDED PROJECTS

PROJECT TITLE: The Molecular Basis of Parkinson's Disease in Saudis
RAC# 2110035
NCPST KACST Project 11-BIO1440-20

INVESTIGATORS: *Al Tassan N, AlKairallah T, Bohlega S, Mubarak B*

PROJECT DESCRIPTION: This funded project by King Abdulaziz City for Science and Technology (KACST), NCPST Program, aims to investigate the molecular basis of Parkinson's disease in patients from Saudi Arabia, using the latest technology in whole exome sequencing.

PROJECT PROGRESS: Screening for the reported genes was completed in ~100 AD, AR and /sporadic index cases. Causative SNV and CNV variants were identified and validated. Targeted sequencing using the SHGP nuero panel identified novel variants in 3 families. Exome sequencing of index cases was performed in the Saudi Human Genome Program Lab, analysis is completed and validation of potential pathogenic variants is ongoing.

PROJECT TITLE: The Molecular Basis of ADHD in Saudi Arabia
RAC # 2120001
NCPST KACST Project 12-BIO2346-20

INVESTIGATORS: *Al Tassan N, Ghaziuddin M, Monies D, Wakil S, Meyer B, Abebe D*

PROJECT PROGRESS: Homozygosity mapping and linkage analysis in AR families with 2 or 3 affected individuals identified novel loci, candidate gene screening is ongoing. Exome Sequencing of Trio's is was completed in the Saudi Human Genome Program Lab. Data was analyzed using different modules of inheritance to identify potential pathogenic SNV's, validation is ongoing in remaining family members.

SELECTED ACHIEVEMENTS FOR 2015

- Identification and characterization of *COL25A1* as a gene mutated in CCDD.

RESEARCH PUBLICATIONS

- Shinwari J, Khan A, Awad S, Shinwari Z, Alaiya A, Alanazi M, Tahir A, Poizat C, Al Tassan N: Recessive Mutations in COL25A1 are a Cause for Congenital Cranial Dysinnervation Disorder. *AJHG*, 2015 Jan 8;96(1):147-52.
- Al-Mubarak, B. R., S. A. Bohlega, T. S. Alkhairallah, A. I. Magrashi, M. I. AlTurki, D. S. Khalil, B. S. AlAbdulaziz, H. Abou Al-Shaar, A. E. Mustafa, E. A. Alyemni, B. A. Alsaffar, A. I. Tahir and N. A. Al Tassan (2015). Parkinson's Disease in Saudi Patients: A Genetic Study. *PLoS One* 10(8): e0135950.
- Adi, A., B. Tawil, M. Aldosari, J. Shinwari, M. Nester, H. Aldhalaan, H. Alshamrani, M. Ghannam, B. Meyer and N. Al Tassan (2015). Homozygosity analysis in subjects with autistic spectrum disorder. *Mol Med Rep* 12(2): 2307-2312.
- Adi, A., B. B. Abbas, M. A. Hamed, N. A. Tassan and D. Bakheet (2015). Screening for Mutations in ABCC8 and KCNJ11 Genes in Saudi Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI) Patients. *Genes* (Basel) 6(2): 206-215.

CARDIOVASCULAR AND PHARMACOGENOMICS UNIT

HEAD
Nduna Dzimiri, PhD

MEMBERS
Paul Muiya, MSc
Samar El Hawari
Olayan AlBedairy,
Editha Andres
Mohammad Najai*
Daisy Gueco
Nejat Al Mazhar
Moni Nader, PhD *(Adjunct Scientist)*

IN 2015, THE EFFORTS OF THE CARDIOVASCULAR AND Pharmacogenomics Unit have focused on successful completion of its major projects. The largest of these was the genome-wide association study on coronary artery disease (CAD) and its risk trains, including diabetes, hypertension and dyslipidemic disorders, in ethnic Saudi Arabs. In its final stage, the study had enrolled >6000 individuals with either CAD, or one of the risk traits. In brief, the study identified a number of predisposing genes/gene variants for each of the traits. In summary, at least 8 genes, *C9orf84*, *CDKN2A/B*, *TRPA1*, *DCLK2*, *KCNAb1* and *PLC1* were linked to disease in the population, whereby the *CDKN2A/B* was equally implicated in myocardial infarction. Additionally another six genes *RNF13*, *PDZD2*, *ITGA1*, *YTHDF3*, *EIFA3* and *KCNE2* were also independently implicated in myocardial infarction. Interestingly, the dyslipidemic traits, such as elevation in low density lipoprotein (LDL)-cholesterol, hypertriglyceridemia (TG), and harbouring of low high density lipoprotein (HDL)-cholesterol (LHDLC) were linked to different genes. These included five genes for TG, eleven for LHDL ten for HT and another eleven for hypercholesterolemia (HL). Of these, variants in the CEPT stood out for LHDLC while those in the APOA1 stood out for TG, as very remarkably associated with disease. Studies on type 2 diabetes mellitus also identified seven predisposing genes in our study population. By far the majority of the implicated genes have not been described in conjunction with these traits yet, pointing to the novelty of the findings.

PROJECT TITLE: Evaluation of the relevance of single nucleotide polymorphism for coronary artery disease in the Saudi population
RAC# 2010020

INVESTIGATORS: *Nduna Dzimiri, Maie Al-Shahid and Brian Meyer*

PROJECT DESCRIPTION: This study examines the role of gene polymorphism(s) in CAD and its risk traits in ethnic Saudi Arabs as a study model. This is accomplished by employing both whole genome scanning approach using the Affymerix Axion platform and targeted gene studies using Taqman assays on the ABI real-time PCR system in a population of >6,000 individuals. These individuals may be harbouring CAD or one or more of the risk diseases, such as hypertension, type 2 diabetes and dyslipidaemia.

PROGRESS: In 2015, we focused primarily on completing the analysis our GWAS data with our collaborators at the University of Western Australia. Briefly, we have described variants and haplotypes in several genes that confer risk for the multiple CAD risk traits. A great number of the implicated variants reside in the non-coding genic regions, which is a subject of current interest in our search for signalling mechanisms contributing to complex cardiovascular disease pathways.

PROJECT TITLE: Relevance of Lipid Metabolizing Proteins in the Treatment of Hypercholesterolemia and Coronary Heart Disease
RAC# 2030012

INVESTIGATORS: *Nduna Dzimiri, Maie Shahid and Brian Meyer*

PROJECT DESCRIPTION: This Project addresses the genetic causes of early onset CAD linked to dyslipidaemia, as well as intra-individual differences in patient responses to drug therapy of antihyperlipidaemia treatment with statins (lipid lowering agents). We employ both linkage studies for early onset of CAD using Affymetrix whole genome scan 250 sty1 array and population-based association analysis on our CAD patients by Taqman assays on the ABI system.

PROGRESS: Linkage studies thus far in eight Saudi families with heterozygous familial hypercholesterolemia (HFH) have yielded a wealth of information regarding possible loci linking early onset CAD with familial hypercholesterolaemia. Data is currently being prepared for public dissemination.

PROJECT TITLE: Role of the Scaffold Protein Striatin in Regulating Cardiac Remodelling
RAC# 2100026

INVESTIGATORS: *Moni Nader, Nduna Dzimiri and Dana Bakheet*

PROJECT DESCRIPTION: Striatin is a scaffold protein which harbours dynamic stretches including (a) coiled-coil motif, (b) eight WD repeats, (c) caveolin binding domain and (d) calmodulin binding sites. The protein assists in the assembly of membrane signalling complexes by anchoring to the oestrogen receptor and eventually modulating signal transduction in vascular endothelial cells. It also probably serves as a scaffold protein within a multicomplex network of kinases and phosphatases primarily consisting of Mob3, GCK, CCM and PP2A, involved in mutlifunctional roles within the cell (i.e. cell death, cell growth, proliferation, cell cycle). During cardiac development, cardiomyocytes stop dividing shortly after birth and undergo enormous changes including increased cell size. This is facilitated by activation of signalling cascades and regulatory proteins involving growth receptors, protein synthesis and calcium homeostasis. Similarly, the foetal gene program is re-activated following myocardial infarction, thus leading to hypertrophy and consequently

impaired cardiac function. Although striatin is present in different tissues, there has been a dearth of information on its presence and/or role in cardiomyocytes. It is also thought that, signalling pathways regulated by striatin partners are activated during cardiac remodelling and/or contraction. For example, aberrant activation of the oestrogen receptor, thought to activate the MAP kinase pathway, leads to cardiomyocyte growth and hypertrophy triggering cardiac dysfunction, therefore suggestive of a pivotal role for striatin myocardial remodelling. Some recent reports have also shown an association of arrythmogenic right ventricle tachycardia with a deletion of the 3' untranslated region of striatin gene resulting in reduced mRNA production, while biochemical analysis revealed that the interaction between striatin and calmodulin or caveolin is calcium sensitive. This is suggestive of an important role for striatin in regulating cardiomyocytes dynamics.

Having successfully identifying striatin in the heart, we moved on to evaluate its role in the evolution of cardiac remodeling by studying its expression level during normal cardiac development with emphasis on molecular aspects in regulating myocardial remodelling. We manipulated the striatin levels by knock down and overexpression procedures to evaluate the status of the multi-signalling complex assembled by striatin to better understand the role of this scaffold protein in regulating cardiomyocyte function.

PROGRESS: In this report period, we performed calmodulin pull down assay, and discovered that striatin assemble with PP2A, caveolin-3 as well as the L-type calcium channel in heart lysates. We found that knockdown of STRN in cultured cardiomyocytes (shRNA) prior to the CaM pull down assay potentiates the interaction of caveolin 3 with STRN/CaM/PP2A/LCC complex. In contrast, cardiomyocytes overexpressing STRN and subjected to CaM pull down assay revealed less interaction of caveolin 3 with this complex. Altogether, our data imply that the expression level of STRN modulates the dynamics of the CaM/PP2A/LCC complex and further investigation is warranted to explore the phenotypic aspect of this interaction.

We also established that striatin levels are modulated by adenoviral delivery (overexpression and knockdown) in primary culture of rat cardiomyocytes. The overexpression experiments revealed that striatin levels are critical for maintaining a proper contraction of cardiomyocytes. We are continuing our investigation by downregulating endogenous striatin in cultured cardiomyocytes and assess for calcium homeostasis and contractility. Knockdown of STRN in cultured cardiomyocytes reduced their contraction rate by about 50%. We attempted to improve the contraction rate by pharmacologically increasing the activity of the calcium channel through beta-adrenergic stimulation (isoproterenol-ISO). ISO failed to improve the contraction rate of cardiomyocytes in lower STRN (shRNA) concentrations compared to control cells (infected with scrambled shRNA). These data strongly suggest that striatin levels are critical for maintaining β-adrenergic stimulation of the LCC. We also demonstrated that striatin interacts with the calcium binding protein calmodulin in a calcium sensitive way in cardiac lysates. Furthermore, striatin form a complex with SLMAP, a membrane protein involved in regulating the excitation-contraction module in the heart, and is associated with a network of proteins (~35 potential targets) in the heart, a notion we are currently chasing.

PUBLICATIONS

ORIGINAL PEER-REVIEWED FULL-LENGTH PUBLICATIONS

- Wakil SM, Ram R, Nguyen C, Muiya NP, Andres E, Mazhar N, Baz B, Hagos S, Alshahid M, Meyer BF, Morahan G, Dzimiri N.. A genome-wide association study reveals novel susceptibility loci for myocardial infarction/coronary artery disease in Saudi Arabs, *Atherosclerosis*, 10.1016/j.atherosclerosis.2015.11.019, 2015.
- Saudi Mendeliome Group. Comprehensive gene panels provide advantages over clinical exome sequencing for Mendelian diseases. *Genome Biology*, Jun 26;16:134. doi: 10.1186/s13059-015-0693-2, 2015.
- Al-Samhari MM, Al-Rasheed NM, Al-Rejaie S, Al-Rasheed NM, Hasan I, Mahmoud AM, Dzimiri N. Possible involvement of the JAK/STAT signaling pathway in N-acetylcysteine-mediated antidepressant-like effects. *Experimental Biology and Medicine*, Dec 6. pii: 1535370215619707, 2015.
- Al-Rasheed MM, Alzahrani AS, Macadam A, Overall A, Gard P, Dzimiri N. The potential role of the sodium iodide symporter gene polymorphism in the development of differentiated thyroid cancer. *Gene*, doi.10.1155/2015/542543, 2015.
- Wakil SM, Nguyen C, Muiya NP, Andres E, Lykowska-Tarnowska A, Baz B, Tahir AI, Meyer BF, Morahan G, Dzimiri N. The Affymetrix DMET plus platform reveals unique distribution of ADME-related variants in ethnic Arabs. *Dis Markers*, doi: 10.1155/2015/542543. Epub 2015 Feb 22.2015.

ABSTRACTS AND SCIENTIFIC CONFERENCE PROCEEDINGS

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- Dasouki MJ, Muiya NP, Andres E, Abouelhoda MM, Nader M and Dzimiri N. Striatin is a novel risk gene for human dilated cardiomyopathy. American Society of Human Genetics, Baltimore, October 6–10, 2015.
- Dzimiri N, Wakil SM, Muiya NP, Andres E, Hagos S, Aldusery H, Dasouki M. High yield of copy number variations in individuals with complex congenital heart disease in Saudi Arabs. European Society of Human Genetics, Glasgow, UK, June 6–9, 2015
- Al-Rasheed MM, Alzahrani AS, Macadam A, Overall A, Gard P, Dzimiri N The TSHβ gene confers risk for differentiated thyroid cancer in the Saudi population. European Society of Human Genetics, Glasgow, UK, June 6–9, 2015.
- Dasouki MJ, Muiya NP, Andres E, Abouelhoda MM, Nader M, Dzimiri N. Striatin is a novel risk gene for human dialted cardiomyopathy. European Society of Human Genetics, Glasgow, UK, June 6–9, 2015.
- Dasouki MJ, Muiya NP, Andres E,Alboudairy O, Abouelhoda MM, Dzimiri N. The clinical utility of a proton ion Ampliseq-based cardiac gene panel. European Society of Human Genetics, Glasgow, UK, June 6-9, 2015.
- Nader M, Al-Gohi A, Hollat J, Khalili B, Kvietys P, Bakheet D, Dzimiri N. Striatin is cleaved during apoptosis in a caspace-3 mediated manner: a step towards novel biomarkers for apoptosis. Experimental Biology, Boston, USA, March 28th–April 1st 2015.
- Nader M, Khalili B, Bakheet D, Dzimiri N, Kvietys P. Silencing of striatin alters he association of caveolin-3 with the L-type calcium channel in cardiomyocytes. Experimental Biology, Boston, USA, March 28th–April 1st 2015.
- Tayeb HT, Arafah MA, Bakheet DM, Khalaf DM, Tarnowksa A, Dzimiri N. Prevalence of CYP2D6 and its implications for personalized medicine in Saudi Arabs. ICHG 2015 XIII International Conference on Human Genetics, London, UK, January 16–17, 2015

COGNITIVE GENETICS UNIT

HEAD

Namik Kaya, MSc, PhD

MEMBERS

Mazhor Salem AlDosary MSc, PhD

AlBandary AlBakheet MSc

Maysoon Alsagob MSc *(Grant Employee)*

Rawan Almas *(Grant Employee)*

Faten Almutairi *(Grant Employee)*

Laila Alquait *(Grant Employee)*

RECENT PROGRESS IN MOLECULAR BIOLOGY PARTICULARLY IN genetics is reshaping the perception and practice of neurology, psychiatry, and behavioral sciences. The application of the new molecular biology techniques such as high-density microarrays and next-generation sequencing to the field of genetic diseases of nervous system and related fields has greatly accelerated our understanding of the mechanisms and pathophysiology of such diseases affecting human body and perception. The elucidation the fundamental causes of these genetic diseases and disorders has proved to be more intricate; but striking progress has been made recently.

MISSION AND GOALS

Altogether neurogenetic, neurodevelopmental, psychiatric and behavioral diseases are very common (10:100) in the Kingdom. Our mission is to explore hereditary causes (nuclear and mitochondrial) of these diseases with a special emphasis on providing a base for appropriate genetic testing and genetic counseling to patients and their family members in the Kingdom and Arabian Peninsula. Our long-term goal is to translate this genetic work into biological research directed towards the understanding pathophysiology of these diseases.

Though our unit is recently established, we have initiated several multidisciplinary research projects including international collaborations with Harvard International and Newcastle University in UK. Our current projects focus on positional cloning of genes underlying genetic disorders with prominent neurodevelopmental manifestations, dysmorphia and mental retardation. We also focus on detection of chromosomal abnormalities as well as copy number variations (CNVs) found among patients and normal individuals. One of the exciting projects undertaken by our unit is creation of a database including such malignant and benign CNVs.

RESEARCH PROJECTS

1. Molecular Studies on Hereditary Ataxias in Saudi Arabia: A Multicenter Study Utilizing Exome Sequencing Coupled with Homozygosity Mapping for Clinical and Diagnostic Use (KACST#14-MED2007-20)
2. Identification of Genes/Mutations Involving Neurologic Disorders (RAC# 2120022).
3. Molecular Studies on Mitochondrial Diseases in Saudi Arabia (KACST#11-BIO2221-20).
4. The Saudi-Arab diseasome -a network of diseases: A comprehensive integrated network-based analysis using genomic, transcriptomic and proteomic data sets for identification of potential markers for diagnosis, prognosis, and therapeutic outcome for Saudi diseases (KACST#11-BIO2072-20)
5. Positional Cloning of Genes Underlying Genetic Disorders with Prominent Neurodevelopmental Manifestations in Several Extended Families (RAC# 2060 035).
6. Molecular Genetic Studies in Chromosome Disorders (RAC# 2040 042).
7. Genetic Basis of Mental Retardation in Families from KSA (RAC# 2080-036).

SELECTED ACHIEVEMENTS

- Awarded as PI by KFSHRC as winner of the 2013 Best Publication Awards.
- Awarded as PI by KFSHRC as winner of the 2011 Best Publication Awards.
- Awarded as PI by KFSHRC as winner of the 2010 Best Publication Awards.
- Awarded as Co-I by KFSHRC as winner of the Best Publication Awards starting from 2008-2013.

LIST OF CURRENT GRADUATE STUDENTS

1. Albandary AlBakheet, PhD Student (Current)
2. Lina Alneghery, PhD Student (Current)
3. Ghada Abohmeid, PhD Student (Current)
4. Nahida Alfuraih, MSc Student (Current)
5. Lama Almahlasi, MSc Student (Current)
6. Razan Alsalamah, MSc Student (Under Acceptance)
7. List of Former Graduate Students
8. Dalia Domiaty, PhD (Graduated)
9. Hind Alosimi, MSc (Graduated)
10. Dalia Alsarar, MSc (Graduated)
11. Nada Alahmed, MSc (Graduated)

12. Fadwa Balawi, MSc (Graduated)
13. Huda AlQahtani, MSc (Graduated)

RECENT PUBLICATIONS

BOOK CHAPTERS AND REVIEW ARTICLES

- Surendran S, Kaya N, Ozand PT, Canavan Disease: Molecular Pathology, Phenotype and Therapeutic Approaches. In: Neurochemistry of Metabolic Diseases Editors: Sankar Surendran, ISBN 978-1-61209-671-1, © 2011 Nova Science Publishers Inc.
- Colak D and Kaya N "Molecular Genetics and Genomics of Hepatocellular Carcinoma", in Liver Tumors, ISBN 979-953-307-069-7 Book edited by: Dr. Ezio Laconi, 2011, InTech Open Access Publisher.
- AlSagob M, Colak D, Kaya N. Genetics of autism spectrum disorder: an update on copy number variations leading to autism in the next generation sequencing era. Discov Med. 2015 May;19(106):367-79. (Invited Review).
- Al-Harazia O, Al Insaifa S, Al-Ajlana MA, Kaya N, Dzimiri N, Colak D. Integrated Genomic and Network-Based Analyses of Complex Diseases and Human Disease Network. Journal of Genetics and Genomics, In Press, Accepted Manuscript, Available online 15 December 2015 doi:10.1016/j.jgg.2015.11.002.

OBITUARY

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PEER REVIEWED JOURNAL ARTICLES

- Al-Hassnan ZN, Shinwari ZM, Wakil SM, Tulbah S, Mohammed S, Rahbeeni Z, Alghamdi M, Rababh M, Colak D, Kaya N, Al-Fayyadh M, Alburaiki J. A substitution mutation in cardiac ubiquitin ligase, FBXO32, is associated with an autosomal recessive form of dilated cardiomyopathy. *BMC Med Genet*. 2016 Jan 14;17(1):3. doi: 10.1186/s12881-016-0267-5.
- Al-Hassnan Z N, Al-Dosary M, Alfadhel M, Faqeih E A, Kenana R, Alsagob M, Almas R, Al-Harazi O S, Al-Hindi H, Malibari O I, Almutari F B, Al-Sheddi T, Tulbah S, Alhadeq F, Alamro R, AlAsmari A, Almuntashri M, Alshaalan H, Al-Mohanna F A, Colak D, Kaya N. ISCA2 mutation causes infantile neurodegenerative mitochondrial disorder. *JMG* 2014 Dec 24. pii: jmedgenet-2014-102592. doi: 10.1136/jmedgenet-2014-102592. [Epub ahead of print].
- Al-Qattan SM, Wakil SM, Anazi S, Alazami AM, Hagos S, Saleh M, El Khashab H, Kaya N, Hashem MO, Alkuraya FS. The Clinical Utility of Molecular Karyotyping for Neurocognitive Phenotypes in a Consanguineous Population. *GiM* 2014 Dec 11. doi: 10.1038/gim.2014.184. [Epub ahead of print].
- Alazami AM, Patel N, Shamseldin HE, Aldosari M, Anazi S, Alzahrani F, Alshammari M, Aldahmesh MA, Hijazi H, Salih MA, Faqeih E, Alhashem A, Bashiri F, Al-Owain M, Kentab A, Sogaty S, Tale S, Temsah H, Tulba M, Julaify R, Shahwan S, Seidahmed MZ, Hadeed A, Dhalaan H, Qallaf F, Kurdi W, Alfadhe M, Habib Z, Alsogheer M, Kaya N, AlHassnan Z, Abdessalam G, Alsannaa N, Jia X, Nguyen HC, Hammami R, Mohamed JY, Abdulwahab F, Ibrahim N, Meyer B, Adly N, Hashem M, Xiong Y, Aboelhouda M, Monies D, Aldeeri AA, Alkuraya FS. Accelerating Novel Candidate Gene Discovery in Neurogenetic Disorders Through Whole-Exome Sequencing of Prescreened Multiplex Consanguineous Patients. *Cell Reports* 2015 Jan 13;10(2):148-61. doi: 10.1016/j.celrep.2014.12.015. Epub 2014 Dec 31.

- Faiyaz-Ul-Haque M, Al-Sayed MD, Faqeih E, Jamil M, Saeed A, Amoudi MS, Kaya N, Abalkhail H, Al-Abdullatif A, Rashed M, Al-Owain M, Peltekova I, Zaidi SH. Clinical, neuroimaging, and genetic features of L-2-hydroxyglutaric aciduria in Arab kindreds. *Ann Saudi Med*. 2014 Mar-Apr;34(2):107-14. doi: 10.5144/0256-4947.2014.107.
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- Al-Rakan MA, Colak D, Hendrayani SF, Al-Bakheet A, Al-Mohanna FH, Kaya N, Al-Malik O, Aboussekhra A. Breast stromal fibroblasts from histologically normal surgical margins are pro-carcinogenic. J Pathol. 2013 Dec;231(4):457-65. doi: 10.1002/path.4256. *PubMed* PMID: 24009142.
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DEVELOPMENTAL GENETICS

HEAD

Fowzan S Alkuraya, MD (Hons), ABP, ABMGG (Clin Gen and Clin Mol Gen)

MEMBERS

Ranad Shaheen, PhD
Nisha Patel, PhD
Sateesh Maddirevula, PhD
Hanan Shamsheldin
Fatma Al-Zahrani
Mais Hashem
Shams Anazi
Nour Ewida
Ibrahim Niema
Ferdous Abdulwahab
Tarfa Alshidi
Rana Alomar
Eman Alobaid

THE DEVELOPMENTAL GENETICS IS MAINLY FOCUSED ON understanding the molecular genetic control of human development by studying the genetics of human malformation syndromes. Specifically, we are involved in the identification of single gene defects that lead to developmental anomalies by exploiting cutting edge techniques and the special nature of our study population. This work is extremely important academically as it represents important contribution to the functional annotation of the human genome, a daunting but necessary task if we are to unlock the mysteries of the human genome and how it controls normal human embryogenesis. In addition, our research helps families afflicted with these Mendelian forms of developmental anomalies by facilitating the molecular diagnosis, a pre-requisite to the implementation of preventive genetic services, which represents a direct translational benefit of our work.

RESEARCH PROJECTS

PROJECT TITLE: Genetics of Craniofacial Birth Defects in Saudi Arabia

PROJECT DESCRIPTION: This program's aim is to study genetic mutations that lead to craniofacial defects.

PROJECT TITLE: Carrier Phenome Project: A Systematic Approach to Study Contribution of Mendelian Mutations to Common Diseases

PROJECT DESCRIPTION: We aim to systemically investigate carriers of deleterious recessive mutations for possible risk of common phenotypes.

PROJECT TITLE: Positional Cloning of Developmentally Relevant Genes Using Patient with Balanced Chromosomal Rearrangements

PROJECT DESCRIPTION: This is a positional mapping project involves the study of breakpoints in the patients with balanced rearrangements.

PROJECT TITLE: Characterization of Peroxisomal Biogenesis Disorders in Saudi Arabia; Clinical, Biochemical and Molecular Studies

PROJECT TITLE: Genetics of Vision Loss in Saudi Arabia

PROJECT DESCRIPTION: This project aims at deciphering the genetics causes of vision impairment, particularly those that can be attributed to pure developmental aberrations like anterior segment dysgenesis, congenital cataract, etc. in the course of this work, the identified genes are developmentally annotated.

SELECTED ACHIEVEMENTS

ADMINISTRATIVE APPOINTMENTS/LEADERSHIP ROLES

- Member, Scientific Advisory Board, Research Center, King Faisal Specialist Hospital, Dammam, Saudi Arabia
- Member, Award Committee, American Society of Human Genetics
- Member, Scientific Committee, International Rare Disease Research Consortium

EDITORIAL BOARDS

- Clinical Genetics
- Human Genetics
- American Journal of Human Genetics (2012-2014)
- Molecular Genetics & Genomic Medicine
- Co-editor of Clinical Genomics: Practical Applications in Adult Patient Care. McGraw Hill and the American College of Physicians
- Journal of Human Genetics
- Journal of Human Genetic Variation
- Genome Biology

GRANTS

- King Salman Center for Disability Research (2015-P): 1 million SR "merit award" to fund the project "Genetics of Vision Loss". Role: Principal Investigator

PUBLICATION

SELECTED PEER REVIEWED JOURNALS

- Human knockout research: new horizons and opportunities. Alkuraya FS. *Trends Genet*. 2015 Feb;31(2):108-15. doi: 10.1016/j.tig.2014.11.003. Epub 2014 Dec 9. Review.

- Primordial dwarfism: an update. Alkuraya FS. *Curr Opin Endocrinol Diabetes Obes*. 2015 Feb;22(1):55-64. doi: 10.1097/MED.0000000000000121. Review.
- A founder CEP120 mutation in Jeune asphyxiating thoracic dystrophy expands the role of centriolar proteins in skeletal ciliopathies. Shaheen R, Schmidts M, Faqeih E, Hashem A, Lausch E, Holder I, Superti-Furga A; UK10K Consortium, Mitchison HM, Almoisheer A, Alamro R, Alshiddi T, Alzahrani F, Beales PL, Alkuraya FS. *Hum Mol Genet*. 2015 Mar 1;24(5):1410-9. doi: 10.1093/hmg/ddu555. Epub 2014 Oct 30.
- RTTN Mutations Cause Primary Microcephaly and Primordial Dwarfism in Humans. Shamseldin H, Alazami AM, Manning M, Hashem A, Caluseiu O, Tabarki B, Esplin E, Schelley S, Innes AM, Parboosingh JS, Lamont R; Care4Rare Canada Consortium, Majewski J, Bernier FP, Alkuraya FS. *Am J Hum Genet*. 2015 Dec 3;97(6):862-8. doi: 10.1016/j.ajhg.2015.10.012. Epub 2015 Nov 19.
- TLE6 mutation causes the earliest known human embryonic lethality. Alazami AM, Awad SM, Coskun S, Al-Hassan S, Hijazi H, Abdulwahab FM, Poizat C, Alkuraya FS. *Genome Biol*. 2015 Nov 5;16:240. doi: 10.1186/s13059-015-0792-0.
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FIRST ARABIAN HEREDITARY DEAFNESS (FAHD) UNIT

HEAD

Faiqa Imtiaz Ahmad, PhD

MEMBERS

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THE MAIN RESEARCH ASPECT OF THE FAHD UNIT IN THE DEPARTMENT of Genetics, is to try and identify known and novel genes causing hereditary non-syndromic and syndromic hearing loss in the Saudi Arabian population (RAC# 2100 001, KSCDR externally funded project, KACST-2015). We are also co-investigators in a number of RAC approved projects, e.g. investigating the molecular basis of Laron Syndrome (RAC# 2101 034), Familial Pulmonary Fibrosis (RAC# 2120 009), and Congenital Glucose-Galactose Malabsorption: Single Center Experience (RAC # 2141 143) in Saudi Arabian patients. We have active collaborations with various departments (Medical Genetics, Pediatrics, Medicine, OB/GYN, and Gastroenterology) and as a direct result we are significantly involved in providing a primary platform for the design, validation and implementation of molecular diagnostic testing for a large number of inherited diseases of clinically diagnosed patients at KFSH&RC. To date, we have initiated, performed and reported in excess of 1200 patients and their families with over 130 different genetic diseases now available at KFSH&RC. In particular, 60 of these genetic tests are designed to molecularly characterize inherited errors of metabolism. In 2015, under the supervision of Dr. Faiqa Imtiaz, the Molecular Diagnostic Laboratory (MDL) successfully performed and reported 350 prenatal molecular diagnostic tests for over 100 different genetic diseases. Our ultimate goal is to help lay the foundation for preventative measures including carrier testing, counseling, prenatal diagnosis, pre-implantation genetic diagnosis and pre-marital screening.

RESEARCH PROJECTS

PROJECT TITLE: Molecular Characterization of Hereditary Deafness in Saudi Population
RAC# 2100 001 & King Salman Centre for Disability & Research

INVESTIGATORS: *Faiqa Imtiaz, PhD, Mohammad Al-Owain,MD, Khushnooda Ramzan, PhD, Selwa AF Al-Hazzaa, MD*

PROJECT DESCRIPTION: The major objective of this study is to define the genetic basis of autosomal recessive deafness in the Saudi population. To achieve this objective, families segregating profound congenital deafness with an autosomal recessive mode of inheritance were identified from different cities of Saudi Arabia. Informed consent is obtained; blood samples are collected and processed for DNA extraction. Large consanguineous families are a powerful resource for genetic linkage studies of recessively inherited hearing impairment. The main ongoing objective of this study is to identify the most common forms of hereditary deafness, their incidence and distribution in the Saudi population. The benefit of this study is also to provide knowledge and awareness through screening of carrier status and genetic counseling, thereby will have a major impact upon early intervention for and prevention of hereditary deafness.

PROGRESS: The major findings of this study showed that hereditary deafness is genetically very heterogeneous in the Saudi Arabian population, which supports the general consensus of worldwide reports. As the most common locus (DFNB1) was excluded from our population, and as there are a large number of genes known to cause hereditary deafness, we accelerated our efforts into recruiting families with two or more affected individuals to allow us to perform homozygosity mapping and linkage analysis. In total, using this combined approach allowed us to proceed with candidate gene selection from regions of homozygosity (ROH) and linkage regions (calculated in families with three or more affected individuals) we identified the disease-causing mutations in 50 families. In addition, we identified previously unreported loci in families that we hope to investigate further in order to potentially discover a novel-deafness causing genes.

We hope to continue our research in the future by extending the search for pathogenic mutations and identification of possible novel deafness-causing genes using Gene Panel and Next-Generation Sequencing technology (Saudi Human Genome Project). In addition, we are pleased to report that the results of this work has contributed to inductive screening, carrier testing, pre-marital diagnostic and prenatal testing.

PROJECT TITLE: Characterization of the genes underlying Usher Syndrome in Saudi Arabian Population
KACST approved-2 million SAR

INVESTIGATORS: *Khushnooda Ramzan, PhD, Faiqa Imtiaz, PhD, Michael Timms, MD, Mohammed Al-Owain, MD, Selwa Alhazzaa, MD, Zeyad Al-Mahasin, MD*

PROJECT DESCRIPTION:

The Usher (USH) syndrome is an autosomal recessive disorder characterized by congenital sensorineural hearing loss and retinitis pigmentosa (RP). It is the most common form of inherited deaf-blindness with a prevalence of ~ 1/6,000. Three clinical subtypes (USH1-USH3) are defined according to the severity of the hearing impairment, the presence or absence of vestibular dysfunction and the age of onset of RP. USH syndrome is genetically heterogeneous, and to date ten causative genes have been identified. Due to high degree of consanguinity in the Saudi Arabian population, it is expected that the incidence of

autosomal recessive diseases are higher than worldwide rate. There is no epidemiological and genetic database available so far for native Saudis affected with USH syndrome. An early diagnosis of USH syndrome is very important which is possible by comprehensive genetic diagnosis.

Main objective and focus of this study will be to analyze the occurrence of USH gene mutations in clinically diagnosed Saudi patients. Whole Genome SNP genotyping coupled with targeted sequencing of the candidate gene in addition to whole Exome sequencing will be utilized.

The dual sensory loss, particularly the progressive loss of vision, presents multiple challenges for individuals with USH syndrome and their families. The primary benefit of this study will be cataloging population specific mutations and to also enable clinicians to confirm the diagnosis early in life for an individual patient, to screen at-risk family members for carrier testing, improved genetic counseling, prenatal diagnosis and pre-implantation genetic diagnosis. In addition a diagnostic procedure will be established which would help in easy and early diagnosis of the disease for this population in future. This project will add to the teaching/training of new faculty and students and will also enhance the existing genetic screening of the Kingdom and the region.

PROGRESS: The project commenced late 2015.

PROJECT TITLE: Clinical and Molecular Basis of Laron Syndrome Patients in Saudi Arabia
RAC# 2101 034

INVESTIGATORS: *Abdullah Al-Ashwal, MD, Afaf Al-Sagheir, MD, Faiqa Imtiaz, PhD, Mohammad Al-Owain, MD, Alya Qari, MSc*

PROJECT DESCRIPTION: The main aim of this project is to discover the pathogenic mutations underlying Laron Syndrome in Saudi patients with this disease.

PROGRESS: We have currently found the disease-causing mutation in 60 of the 70 patients enrolled in this study. Homozygosity mapping is currently being performed in the remaining 10 patients where the GHR gene was negative to try and identify regions to locate the disease-causing gene(s).

PROJECT TITLE: Clinical and Molecular Characterization of Familial Pulmonary Fibrosis in a Saudi Family
RAC# 2120 009

INVESTIGATORS: *Eid Al-Mutairy, MD, Faiqa Imtiaz, PhD, Mohammad Al-Owain, MD, Abdullah Al-Mubaireek, MD*

PROJECT DESCRIPTION

The main aims of this project are to clinically characterize the unique pulmonary phenotype of the familial pulmonary fibrosis (FPF) in a single Saudi Family and to identify the causative gene through different methods of gene mapping.

PROGRESS: All the members of the Saudi family with FPF were consented and samples were collected and genomewide SNP genotyping was performed using the GeneChip®Mapping Axiom Array and homozygosity mapping/ linkage analysis was conducted.

One major region of linkage/homozygosity was identified that was shared by all 3 affected patients (and not shared by unaffected family members) and did not contain any known FPF-disease causing genes. Sequencing of candidate genes in the region indicated a mutation which segregates in one gene which may be pathogenic. Functional

analysis is currently being carried out in the novel gene identified to confirm pathogenicity.

However, further screening of additional familial and sporadic cases of patients with clinically diagnosed FPF is necessary to confirm initial findings.

PROJECT TITLE: Congenital Glucose-Galactose Malabsorption: Single Center Experience
RAC# 2141 143

INVESTIGATORS: *Khalid Al-Saleem, MD, Yasir Al-Suyufi, MD Ali Al-Mehaidib, MD, Mohammed Banemai, MD, Wajeeh Mohamed Aldekhail,, MD, Faiqa Imtiaz, PhD, Rabab Allam, MSc*

PROJECT DESCRIPTION: The main aim of this project is to discover the pathogenic mutations underlying Congenital Glucose-Galactose Malabsorption (CGGM) in Saudi patients with this disease.

PROGRESS: The pathogenic mutation has been identified in sequencing the SLC5A1 in 20 of 32 patients with CGGM that were clinically diagnosed in the clinic. Further analysis is currently being carried out to try and determine the underlying genetic defect in the patients where SLC5A1 was negative.

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GENE THERAPY UNIT

HEAD

Yufei Shi, PhD

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Essa Baitei

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GENE THERAPY UNIT IS CURRENTLY CONDUCTING EXPERIMENTAL gene therapy research on thyroid cancer, elucidating molecular defects leading to thyroid tumorigenesis, and molecular genetic analysis of genes involved in endocrine disorders. Significant progress has been made on each front. We have established a mouse model of spontaneous thyroid papillary cancer and demonstrated that IL-12 immunotherapy is effective against papillary thyroid cancer (PTC). We have also demonstrated that thyroid stimulation hormone (TSH) has played a significant oncogenic role in promoting thyroid tumorigenesis and preventing oncogene-induced senescence (OIS). Without TSH stimulation, oncogenic Ras would not be able to induce thyroid cancer and established PTC induced by oncognic BrafV600E would go through OIS via p53 dependant mechanism. These data reinforce the importance of rigorous control of serum TSH in PTC patients.

RESEARCH PROJECTS

PROJECT TITLE: IL-12 Gene Therapy of Thyroid Cancer in BRAFV^{600E} Transgenic Mouse Model
RAC#2130 007
KACST biotechnology grant #11-BIO1434-20

INVESTIGATORS: *Yufei Shi, Ranjit S. Parhar, Minjing Zou*

PROJECT DESCRIPTION: Thyroid carcinoma is the second most common malignancy among Saudi female cancer patients. There are three types of thyroid carcinoma derived from thyroid follicular cells: papillary, follicular, and anaplastic carcinomas. Papillary thyroid carcinomas (PTC) are the most common type, accounting for more than 80% thyroid malignancies. BRAF^{V600E} mutations are frequently identified in more than 40% PTC. Although most differentiated thyroid carcinomas can be cured by surgery and ^{131}I therapy, 10-20% patients are refractory to the conventional therapy and die from recurrence or progression into poorly differentiated tumors. No effective treatment is currently available for these patients, making it necessary to develop novel therapeutic approaches. Interleukin 12 (IL-12) is a proinflammatory heterodimeric cytokine with strong antitumor activity. Our previous studies have shown that IL-12 gene therapy is effective against anaplastic thyroid carcinoma in a nude mice xenograft tumor model. In the current project, we plan to investigate IL-12 immunotherapy against BRAF^{V600E} mutation induced thyroid tumors in a transgenic mouse model.

PROJECT PROGRESS: Tumor size and weight were significantly reduced by either weekly intramuscular injection of scIL-12/CMVpDNA or daily intraperitoneal injection of mouse recombinant IL-12, and tumor became more localized. Survival was significantly increased when treatment started at one week of age as compared to that at the 6 weeks of age. Both NK and CD8 T cells were involved in the cytotoxicity against tumor cells and their anti-tumor activity was significantly reduced in tumor-bearing mice. The inhibition was completely reversed by IL-12 treatment and partially recovered by anti-TGF-β antibody.

Both IL-12 gene therapy and recombinant protein therapy are effective against PTC. The anti-tumor activity of host immune cells can be re-activated by IL-12 immunotherapy. The data have been published in Laboratory Investigation.

PROJECT TITLE: Investigation of Sprouty Family of Proteins in Thyroid Cancer Development and Progression
RAC# 2140 023

INVESTIGATORS: *Minjing Zou, Abdullah M. Assiri and Yufei Shi*

PROJECT DESCRIPTION: The Sprouty family of proteins contains 4 members and can antagonize MAPK/ERK signaling cascade, thus functions as a negative feedback regulator of receptor tyrosine kinase (RTK) signaling. Down-regulation of *Spry* gene expression has been reported in many cancers such as hepatocellular carcinoma, non-small cell lung cancer, B-cell lymphoma, neuroblastoma, prostate cancer, and medullary thyroid carcinoma. The *Spry* gene expression has not been well studied in thyroid cancer. In our preliminary study of *Spry1-4* gene expression in 10 thyroid cancer cell lines, we found that *Spry1* expression was significantly reduced in cell lines with BRAF^{V600E} mutation. The expression of *Spry2-4* was not significantly changed. In the present proposal, we plan to study 68 archived thyroid tumor specimens for *Spry1* expression. We would like to investigate whether *Spry1* expression is associated with BRAF^{V600E} mutation and restoration of *Spry1* expression can reduce cancer cell growth. We would also like to create two mouse strains to investigate

the role of *Spry1* in thyroid tumorigenesis: one with concomitant thyroid specific expression of $Kras^{G12D}$ and *Spry1* knockout, and the other with concomitant thyroid specific expression of $BRAF^{V600E}$ and *Spry1* knockout.

PROGRESS: $Kras^{G12D}$ causes lung cancer rapidly, but is not sufficient to induce thyroid cancer. TPO-$Kras^{G12D}$ and TPO-$BRAF^{V600E}$ strains were created, which allow conditional expression of $Kras^{G12D}$ or $BRAF^{V600E}$ in thyroid follicular cells through Cre-mediated deletion of a floxed transcriptional stop sequence. Under chronic TSH stimulation, significant thyroid enlargement and hyperplasia occurred in both TPO-$Kras^{G12D}$ and TPO-$Kras^{WT}$ mice. In contrast, only mild thyroid enlargement and hyperplasia were observed in TPO-$Kras^{G12D}$ mice without treatment. Distinct thyroid histology was found between TPO-$Kras^{G12D}$ and TPO-$Kras^{WT}$ mice: thyroid from TPO-$Kras^{G12D}$ showed follicular hyperplasia whereas in TPO-TPO-$Kras^{WT}$ this structure was replaced by papillary hyperplasia. Among 10 TPO-$Kras^{G12D}$ mice monitored for 14 months, two developed follicular thyroid cancer (FTC), one with pulmonary metastasis. Differential SPRY1 expression was demonstrated: increased in FTC and reduced in papillary thyroid cancer (PTC). The increased SPRY1 expression in FTC caused only PI3K/AKT activation whereas down-regulation of SPRY1 in PTC resulted in both MAPK and PI3K/AKT activation. These data demonstrate that chronic TSH stimulation can promote $Kras^{G12D}$ mediated oncogenesis, leading to FTC. SPRY1 may function as a molecular switch to control MAPK signaling and its down-regulation by $BRAF^{V600E}$ favors PTC development. The data have been published in Laboratory Investigation.

PROJECT TITLE: Role of Thyroid Stimulating Hormone in Preventing Oncogene-induced Senescence
RAC# 2150 002

INVESTIGATORS: *Minjing Zou and Yufei Sh*

PROJECT DESCRIPTION: The RAS–RAF–MEK–ERK MAP kinase signaling pathway (MAPK) plays an important role in the initiation and progression of PTC. Among genetic alterations detected in PTC, $BRAF^{V600E}$ is the most common mutation (44%) and has been associated with poorer prognosis and more aggressive clinical outcome. $BRAF^{V600E}$ can down-regulate the expression of genes (*NIS, TG, TPO*) involved in thyroid hormone synthesis and promote dedifferentiation processes in PTC. In mice with normal serum TSH or blocked TSH signaling, tumorigenesis may occur but is significantly delayed, and tumors are small and localized, indicating that development of aggressive $BRAF^{V600E}$-induced PTC (BVE–PTC) requires constant TSH stimulation. $BRAF^{V600E}$-induced senescence occurs in human and mouse naevi, protecting melanocytes against $BRAF^{V600E}$-driven proliferation and progression into melanoma. This process has not been demonstrated in mouse models of $BRAF^{V600E}$-induced thyroid cancer and elevated TSH may prevent oncogene-induced senescence (OIS). It is known that TSH stimulates the growth and development of thyroid cancer and elevated serum TSH is associated with higher thyroid cancer incidence and recurrence. In the present study, we investigated BVE–PTC progression under normal serum TSH and explored the molecular mechanisms regulating the process.

PROGRESS: To investigate the progression of BVE–PTC under normal TSH, we transplanted subcutaneously BVE–PTC tumors into nude and syngenic wild-type TPO–$Braf^{WT}$ mice. Regression of the transplanted tumors was observed in both nude and TPO–$Braf^{WT}$ mice. They were surrounded by heavy lymphocyte infiltration and oncogene-induced senescence (OIS) was demonstrated by strong β-gal staining and absence of Ki-67 expression. In contrast, BVE–PTC transplants

continued to grow when transplanted into TPO–*BRAF*^{V600E} mice. The expression of *Trp53* was increased in tumor transplants undergoing OIS. *Trp53* inactivation reversed OIS and enabled tumor transplants to grow in nude mice with characteristic cell morphology of anaplastic thyroid cancer (ATC). PTC-to-ATC transformation was also observed in primary BVE–PTC tumors. ATC cells derived from *Trp53* knockout tumors had increased PI3K/AKT signaling and became resistant to *BRAF*^{V600E} inhibitor PLX4720, which could be overcome by combined treatment of PI3K inhibitor LY294002 and PLX4720. In conclusion, BVE–PTC progression could be contained via p53-dependent OIS and TSH is a major disruptor of this balance. Simultaneous targeting of both MAPK and PI3K/AKT pathways offer a better therapeutic outcome against ATC. The current study reinforces the importance of rigorous control of serum TSH in PTC patients. The data have been published in Oncogene.

PROJECT TITLE: Expression of *CYP24A1*, the Catabolizing Enzyme of Vitamin D, in Thyroid Tumor Development and Progression

RAC# 2111 10

KACST biotechnology grant # 13-MED1765-20

INVESTIGATORS: *Minjing Zou, and Yufei Shi*

PROJECT DESCRIPTION: Vitamin D exists in two major forms: ergocalciferol (vitamin D2), and cholecalciferol (vitamin D3). Both forms need two-step hydroxylation at carbons 1 and 25 for activation. 1α, 25$(OH)_2D_3$ (calcitriol), the active form of vitamin D, has been shown to exert antiproliferative effects in many cancers. Vitamin D 24-Hydroxylase (*CYP24A1*) is the primary vitamin D-inactivating enzyme, which catabolizes 1α, 25$(OH)_2$D into inactive 1α, 24,25$(OH)_3$D. Overexpression of *CYP24A1*, the primary vitamin D-inactivating enzyme, is also observed in a variety of human cancers, thus potentially neutralizing the antitumor effect of 1α, 25$(OH)_2D_3$. The diminished anti-tumor effects of calcitriol can be restored by inhibition of *CYP24A1*. In the present study, we will investigate *CYP24A1* expression and *BRAF* mutation in 57 PTC to determine whether *CYP24A1* expression is associated with disease progression and *BRAF* mutation is involved in inducing *CYP24A1* expression. We will also investigate thyroid tumorigenesis in *CYP24A1* knockout mice.

Progress: We investigated 57 papillary thyroid carcinoma (PTC) specimens for *CYP24A1* expression, and its association with *BRAF* mutation and disease progression. *CYP24A1* expression was measured by real-time RT-PCR and *BRAF*^{V600E} mutation was detected by PCR-DNA sequencing analysis. The interaction between *BRAF*^{V600E} and *CYP24A1* expression was determined by Western blot analysis and real-time RT-PCR. *CYP24A1* expression was increased in PTC as compared to benign multinodular goiter. The expression was further increased in stage III and IV tumors. There is a strong correlation between *CYP24A1* overexpression and *BRAF*^{V600E} mutation ($p<0.01$). In thyroid cancer cell lines expressing *BRAF*^{V600E}, *CYP24A1* expression was significantly higher when compared to those without *BRAF*^{V600E} expression. *BRAF*^{V600E} transgene expression in CAL62 cell line can induce *CYP24A1* expression. Furthermore, *BRAF*^{V600E} inhibitor PLX4720 can significantly down-regulate *CYP24A1* expression and enhance the antiproliferative effects of calcitriol in thyroid cancer cell lines. We conclude that *CYP24A1* overexpression is a poor prognostic indicator for PTC and may reflect *BRAF*^{V600E} mutation and MARK activation. The cross-talk between vitamin D and MAPK signaling pathways results in resistance to calcitriol mediated anti-tumor effects and the resistance can be reversed by *BRAF*^{V600E} inhibitor PLX4720.

PUBLICATIONS

- Novel CYP27B1 Gene Mutations in Patients with Vitamin D-Dependent Rickets Type 1A. Demir K, Kattan WE, Zou M, Durmaz E, BinEssa H, Nalbantoğlu Ö, Al-Rijjal RA, Meyer B, Özkan B, Shi Y. *PLoS One*. 2015 Jul 1;10(7):e0131376. doi: 10.1371/journal.pone.0131376.
- A Novel Mutation in the *CYP11B1* Gene Causes Steroid 11β-Hydroxylase Deficient Congenital Adrenal Hyperplasia with Reversible Cardiomyopathy. Alqahtani MA, Shati AA, Zou M, Alsuheel AM, Alhayani AA, Al-Qahtani SM, Gilban HM, Meyer BF, and Shi Y. *Int J Endocrinol*. 2015;2015:595164. Doi:10. 1155/2015/595164. Epub 2015 July 22.
- $KRAS^{G12D}$ -mediated oncogenic transformation of thyroid follicular cells requires long-term TSH stimulation and is regulated by SPRY1. Zou M, Baitei EY, Al-Rijjal RA, Parhar RS, Al-Mohanna FA, Kimura S, Pritchard C, BinEssa H, Alanazi AA, Al-zahrani AS, Akhtar M, Assiri AM, Meyer BF, and Shi Y. *Lab Invest*. 95:1269-77, 2015. Jul 6. doi: 10.1038/labinvest.2015.90. [Epub ahead of print].
- TSH overcomes $Braf^{V600E}$ -induced senescence to promote tumor progression via down-regulation of p53 expression in papillary thyroid cancer. Zou M, Baitei EY, Al-Rijjal RA, Parhar RS, Al-Mohanna FA, Kimura S, Pritchard C, BinEssa H, Alanazi AA, Al-zahrani AS, AlKhalaf, H, Hawwari A, Akhtar M, Assiri AM, Meyer BF, and Shi Y. *Oncogene* 2015, Oct 19. doi:10.1038/onc.2015.253. [Epub ahead of print].
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GENOTYPING CORE FACILITY

HEAD

Salma Wakil, PhD

MEMBERS

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Samya Hagos, BSc

Rula Abothuraya, BSc

Batool Baz, MSc *(on study leave)*

THE MAIN AIM OF THIS UNIT IS TO PROVIDE GENOTYPING FOR DNA Analysis and differential Gene Expression profiling using the Affymetrix GeneChip technology, accelerating the genetic research and enables the researchers to develop the diagnostic tools and tailor treatments for individual patients by identifying and measuring the genetic information associated with mendelian and complex disorders.

The laboratory is genotyping approx. 1000 samples in a month with Axiom Genome Wide Human Array plate assay which is optimized for candidate gene studies, genome wide association studies and replication studies. We are running the cytogenetic microarray, a high resolution array to detecting broad range of chromosomal aberrations, detects uni-parental disomy and regions that are identical by descent. A large number of samples are being genotyped for molecular karyotyping with this microarray. Besides DMET microarray which is comprehensively used to detect the pharmacogenetic markers for drug metabolism studies is being routinely carried out at the laboratory. Also we are involved with miRNA array, is a powerful tool for studying the regulatory mechanisms mediated by miRNAs and their importance in cancer and other diseases. The miRNA studies facilitate the discovery of biomarkers and disease signatures. Recently we have started working with FFPE cancer samples investigating the biology underlying rare tumor types, complex malignant processes, such as metastatic progression, and long-term clinical outcome studies. For this purpose we are using SNP based microarray called oncoscan which uses molecular inversion technology for identifying copy number changes, loss of heterozygosity and detecting somatic mutations in samples with limited amounts of highly modified and degraded DNA. This assay is well suited for cancer clinical research.

RESEARCH PROJECTS

PROJECT TITLE: Molecular Genetic Characterization of Hereditary Spastic Paraplegias (HSPs)

PROJECT DESCRIPTION: Hereditary Spastic Paraplegia is a neurodegenerative disorder, which affect the upper motor neurons resulting in long term disability and early death. It encompass clinically and genetically heterogeneous group. It can be a pure or complex sub-type. Spasticity is the major presenting feature. The prevalence of HSP among Saudis has expected to be high due to high degree of consanguinity as recorded in our neuromuscular database. We expect to classify the Saudi patients affected with HSP into different genetic sub-types. Also to discover new genes associated with HSP in the local Saudi population. We will be using homozygosity mapping, genetic linkage and DNA sequencing. Discovering such new gene/genes will help in understanding HSP pathophysiology and hopefully treatment options also will provide prenatal as well as postnatal genetic counseling for these HSP families.

PROGRESS: Thirty five families have been collected for this project. We have been able to underline novel mutations for many families so far. It has been observed that SPG11 loci underlines for more than 50 percent of the HSP cohort in our study. Apart, we have also detected novel genes in our study.

PROJECT TITLE: Molecular Genetic Characterization of Dermatological disorders

PROJECT DESCRIPTION: Skin is a major sensory organ that protects the body from major environmental insults. It comprises of various cell types facilitating intercellular interactions maintaining the structural integrity of the skin. Advancement in the field of molecular biology together with advent of new technologies (e.g. next generation sequencing) has led to identification of increasingly large number of gene defects responsible for a wide spectrum of phenotypic manifestations in various skin disorders. Genetic skin disorders are poorly characterized in Arab populations. There is high prevalence of genodermatosis among Arabs due to high rate of consanguinity and endogamy. We aim to describe the predominant forms of genetic skin disorders in Arabs and identify the

molecular defects underlying the various subtypes of these disorders. Using the combined approach Homozygosity tools together with next generation sequencing has been shown to be highly efficient in identifying the genetic etiology of skin disorders, particularly in cases where there are multiple family members affected. Identifying causative genetic variants will be helpful in genetic counseling and offering preventative measures like prenatal and preimplantation genetic diagnosis for the patients with diverse skin disorders. A large number of families for various heritable skin disorders are being screened under this project.

PROJECT TITLE: Molecular Characterization of Amyotrophic lateral sclerosis (ALS)

PROJECT DESCRIPTION: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that affects the upper and lower motor neurons resulting in disability and death due to respiratory insufficiency within few years from onset. It is the most common form of adult onset motor neuron degeneration. Approximately 90% of ALS individuals have no family history of ALS (Sporadic ALS, SALS), the remaining 10% have at least one other affected family member (Familial ALS, FALS. Amyotrophic lateral sclerosis affects 1-3 per 100,000 Caucasians and expected to affect similar numbers in Saudi Arabian population7. Given the prevalence of ALS and the current limited knowledge about the genetics of this disorder in the Saudi population we expect to discover novel genes/ mutations associated with the pathogenesis of ALS in the local population. This would be attainable using homozygosity mapping, genetic linkage and DNA sequencing. Discovering new ALS genes would be one of the initial steps towards understanding ALS pathophysiology and thereafter treatment modalities. We have identified a number of novel mutations in ALS2 gene in sporadic cases among a cohort of 60 sporadic ALS patients. In many of the samples, we have identified blocks of homozygosity where gene screening will be prioritized.

PROJECT TITLE: Localization of Familial Juvenile Rhematoid Arthritis

PROJECT DESCRIPTION: The objective of this study was to perform Homozygosity mapping and use positional candidate gene approach to identify the gene underlying this novel syndrome. So far based on the four families we performed the whole genome scan using affymetix arrays, we identified a homozygous region on chromosome 13 for all the affected individuals. We identified a novel mutation in a novel gene for this disorder. And the work so far accomplished was published in high impact factor of the field.

PROJECT TITLE: Assessing the Genotype's Distribution of Genetic Polymorphic Variations and their Impact on the Risk of Radiation Exposure in Saudi Individuals

PROJECT DESCRIPTION: This project is in collaboration with Radiation Biology Section, Research Center.

PROJECT TITLE: Relevance of Lipid Metabolizing Proteins in the Treatment of Hypercholesterolemia and Coronary Heart Disease

PROJECT DESCRIPTION: This project is in collaboration with Cardiovascular and Pharmacogenomics Section, Research Center where variants for disorders of dyslipidemia are identified through linkage studies and direct sequencing.

PROJECT TITLE: Evaluation of the Relevance of Single Nucleotide Polymorphism for Coronary Artery Disease in the Saudi Population

PROJECT DESCRIPTION: This project is in collaboration with Cardiovascular and Pharmacogenomics

Section, Research Center where large group of Coronary Artery Disease patients and controls are genotyped for Genome wide association studies for identification of susceptible SNPs.

RESEARCH PUBLICATIONS

- Abnormalities of skin and cutaneous appendages in neuromuscular disorders. Josef Finsterer, Salma Wakil. *Pediatric Neurology*. 2015. Oct;53(4):301-8.
- A genome-wide association study reveals susceptibility loci for myocardial infarction/ coronary artery disease in Saudi Arabs. Wakil SM, Ram R, Muiya NP, Mehta M, Andres E, Mazhar N, Baz B, Hagos S, Alshahid M, Meyer BF, Morahan G, Dzimiri N. *Atherosclerosis*. 2015 Nov 22;245:62-70.
- Mitochondrial implications in bulbospinal muscular atrophy (Kennedy disease). Finsterer J, Mishra A, Wakil S, Pennuto M, Soraru G. *Amyotroph Lateral Scler Frontotemporal Degener*. 2015 Oct 1:1-7.
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- A new GWAS and meta-analysis with 1000Genomes imputation identifies novel risk variants for colorectal cancer. Al-Tassan NA, Whiffin N, Hosking FJ, Palles C, Farrington SM, Dobbins SE, Harris R, Gorman M, Tenesa A, Meyer BF, Wakil SM, Kinnersley B, Campbell H, Martin L, Smith CG, Idziaszczyk S, Barclay E, Maughan TS, Kaplan R, Kerr R, Kerr D, Buchannan DD, Ko Win A, Hopper J, Jenkins M, Lindor NM, Newcomb PA, Gallinger S, Conti D, Schumacher F, Casey G, Dunlop MG, Tomlinson IP, Cheadle JP, Houlston RS. *Sci Rep*. 2015 May 20;5:10442.
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- Genotyping of CYP2C19 polymorphisms and its clinical validation in the ethnic Arab population. Tayeb HT, Bakheet DH, Zaza K, Wakil SM, Dzimiri N. *J Pharm Pharmacol*. 2015 Jul;67(7):972-979.
- A novel APC mutation defines a second locus for Cenani-Lenz syndrome. Patel N, Faqeih E, Anazi S, Alfawareh M, Wakil SM, Colak D, Alkuraya FS. *J Med Genet*. 2015 May;52(5):317-21.
- The Affymetrix DMET Plus Platform Reveals Unique Distribution of ADME-Related Variants in Ethnic Arabs. Wakil SM, Nguyen C, Muiya NP, Andres E, Lykowska-Tarnowska A, Baz B, Tahir AI, Meyer BF, Morahan G, Dzimiri N. *Dis Markers*. 2015.

- The clinical utility of molecular karyotyping for neurocognitive phenotypes in a consanguineous population. Al-Qattan SM*, Wakil SM*, Anazi S*, Alazami AM, Patel N, Shaheen R, Shamseldin HE, Hagos ST, AlDossari HM, Salih MA, El Khashab HY, Kentab AY, AlNasser MN, Bashiri FA, Kaya N, Hashem MO, Alkuraya FS. *Genet Med*. 2015 Sep 2;17(9):719-25.

- Association of a mutation in LACC1 with a monogenic form of systemic juvenile idiopathic arthritis. Wakil SM, Monies DM, Abouelhoda M, Al-Tassan N, Al-Dusery H, Naim EA, Al-Younes B, Shinwari J, Al-Mohanna FA, Meyer BF, Al-Mayouf S. *Arthritis Rheumatol*. 2015 Jan;67(1):288-295.

IMMUNOGENETICS

HEAD
Anas Alazami, PhD

MEMBERS
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Lina El-Baik
Afaf Al-Otaibi

OUR SECTION CONCENTRATES ON THE GENETIC CAUSES OF immunodeficiency in Saudi Arabia. Dysregulation of a wide array of immune system genes can lead to many debilitating diseases such as immune deficiencies, cancer and autoimmunity. Through the use of high throughput genotyping, and targeted next generation sequencing (gene panels and exome analysis) we aim to identify deleterious mutations that are segregating in the population. Our cases range from severe combined and combined variable immunodeficiency to the hyper-immunoglobulinopathies to disorders with sizeable overlap across disciples. This extensive collection is exciting as it provides us with the opportunity, not only of offering service to patients and their families, but also to focus on novel findings for immune genes which have not yet been linked to a specific disorder, for the wider benefit of the clinical and scientific communities.

RESEARCH ACTIVITY

PROJECT TITLE: Underlying molecular genetic defects of Primary Immunodeficiency Diseases in Saudi Arabia
RAC# 2080 025

INVESTIGATORS: *Dr. Hamoud Al-Mousa, Safa Al-Hissi, Lina El Baik, Afaf Al-Otaibi, Dr. Dorota Monies, Dr. Abdulaziz Al-Ghonaium, Dr. Hasan Al-Dhekri, Dr. Saleh Al-Muhsen, Dr. Rand Arnaout, Dr. Bandar Al-Saud, and Dr. Anas Alazami*

PROJECT DESCRIPTION AND PROGRESS: There is a wide variety of primary immunodeficiency diseases (PIDs) that are caused by congenital defects of the immune system. To this day over 100 inherited PIDs are known to exist, with an incidence estimate of 1 in 10,000 to 1 in 2000 among live births. These include X-linked agammaglobulinemia (Bruton's Disease), common variable immune deficiency (CVID), selective IgA deficiency, and severe combined immune deficiency (SCID). PIDs result from defects in T-, B-, NK-, phagocytic cells or the complement system. Certain PID types like CVID and selective IgA deficiency are not always familial; their cause is unknown but the interaction of genetic and environmental factors may play a role in their causation. If untreated, PIDs may associate with frequent life-threatening infections and debilitating illnesses. The genes responsible for most of these diseases have been identified due to modern advances in molecular diagnostics, which enable early disease detection and adequate treatment. Mutation detection approaches are available to identify mutations through genotyping and direct sequencing. As would be expected, the incidence of these disorders in Saudi Arabia is higher than the world average due to the high rate of consanguinity, and there is a need to delineate the molecular bases underlying them. Based on our experience we have identified a substantial number of novel mutations, and are currently assessing several cases that are negative for known genes using next generation sequencing, with the aim of uncovering novel loci/genes that have yet to be implicated in human disease. Results emanating from these studies will benefit patients and their families in terms of counseling, pre-implantation genetic diagnosis, and prenatal diagnosis.

This past year our section spearheaded or participated in the following papers:

- Hematopoietic stem cell transplant for hyper-IgM syndrome due to CD40L defects: A single-center experience. Al-Saud B, Al-Mousa H, Al-Ahmari A, Al-Ghonaium A, Ayas M, Alhissi S, Al-Muhsen S, Al-Seraihy A, Arnaout R, Al-Dhekri H, Hawwari A. *Pediatr Transplant*. 2015 Sep;19(6):634-9.
- Comprehensive gene panels provide advantages over clinical exome sequencing for Mendelian diseases. Saudi Mendeliome Group. *Genome Biol*. 2015 Jun 26;16:134.
- DOCK8 deficiency: clinical and immunological phenotype and treatment options - a review of 136 patients. Aydin SE, Kilic SS, Aytekin C, Kumar A, Porras O, Kainulainen L, Kostyuchenko L, Genel F, Kütükcüler N, Karaca N, Gonzalez-Granado L, Abbott J, Al-Zahrani D, Rezaei N, Baz Z, Thiel J, Ehl S, Marodi L, Orange JS, Sawalle-Belohradsky J, Keles S, Holland SM, Sanal Ö, Ayvaz DC, Tezcan I, Al-Mousa H, Alsum Z, Hawwari A, Metin A, Matthes-Martin S, Hönig M, Schulz A, Picard C, Barlogis V, Gennery A, Ifversen M, van Montfrans J, Kuijpers T, Bredius R, Dückers G, Al-Herz W, Pai SY, Geha R, Notheis G, Schwarze CP, Tavil B, Azik F, Bienemann K, Grimbacher B, Heinz V, Gaspar HB, Aydin R, Hagl B, Gathmann B, Belohradsky BH, Ochs HD, Chatila T, Renner ED, Su H, Freeman AF, Engelhardt K, Albert MH; inborn errors working party of EBMT. *J Clin Immunol*. 2015 Feb;35(2):189-98.

NEWBORN SCREENING & BIOCHEMICAL GENETICS LABORATORY

HEAD

Majed Dasouki, MD

MEMBERS

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Fatima Al Hejji
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NSBGL IS A CLINICAL BIOCHEMICAL DIAGNOSTIC & SCREENING lab which performs various biochemical genetic assays as well as newborn screening for multiple inborn errors of metabolism. We currently perform ~75,000 newborn screening assays annually. We also conduct research in biochemical genetic disorders & develop new assays to be implemented in expanded newborn screening. We educate our clients (referring hospitals, labs & physicians) on the process of newborn screening & biochemical genetic testing.

RESEARCH PROJECTS

- Development of Population-Based Newborn Screening for primary Immunodeficiency Diseases in Saudi Arabia.
- The Genetic Basis of "Acquired" Aplastic Anemia in Saudi Arabia
- Development of Population-Based Newborn Screening for Cystic Fibrosis in Saudi Arabia.

ACHIEVEMENTS OF NSBGL IN 2015 INCLUDE:

- An additional disorder which is Very Long-Chain Acyl-CoA Dehydrogease Deficiency (VLCAD) was added to the screening panel giving a total of 17 disorders included in the program (see Table 1).
- Five additional Hospitals have joined the program resulting in a total of more than 150 participating hospitals.
- Total number of newborns screened during 2015 was 75,288. The distribution of the samples is shown in Figure 2.
- Total # of Abnormal cases detected was 54 cases. The distribution of detected cases per region is illustrated in Figure 3. The detected disorder is demonstrated in Figure 4.
- Total number of sick babies samples "MS/MS profile" run in 2015 was 9154.
- Number of samples received from major hospitals participating in the program is illustrated in Figure 5.

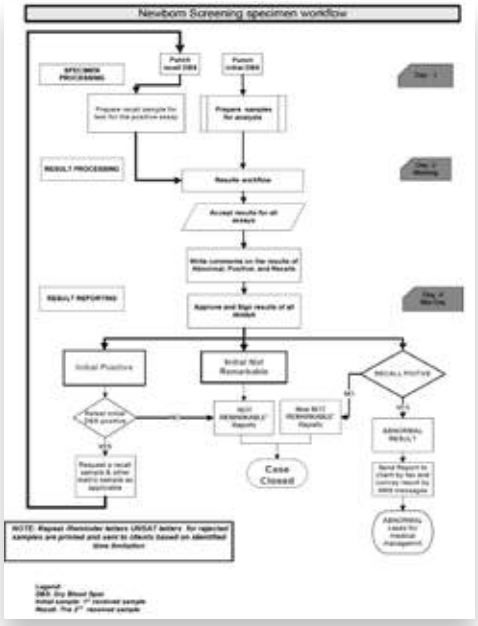

Figure 1: The newborn screening workflow.

Table 1: Disorders included in the Newborn Screening Panel.

Phenylketonuria (PKU)
Maple Syrup Urine Disease (MSUD)
Argininosuccinate Lyase deficiency (ASL)
Citrullinemia (CIT)
Propionic Acidemia (PPA)
Methylmalonic Acidemia (MMA)
Glutaric Acidemia type-I (GA-I)
Isovaleric Acidemia (IVA)
3-Methylcrotonyl-CoA Carboxylase Deficiency (3 MCC)
Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)
Very Long-Chain Acyl-CoA Dehydrogease Deficiency (VLCAD)- Newly added
3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency (HMG)
Beta-Ketothiolase Deficiency (BKT)
Biotinidase Deficiency (BTD)
Galactosemia (GALT)
Congenital Hypothyroidism (CH)
Congenital Adrenal Hyperplasia (CAH)

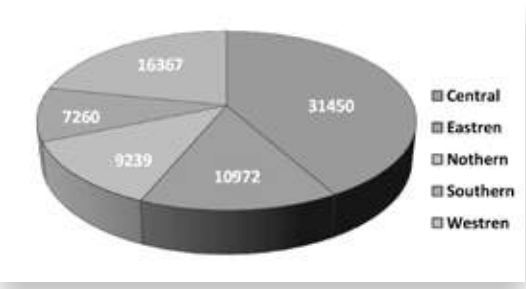

Figure 2: Total number of samples received in 2015.

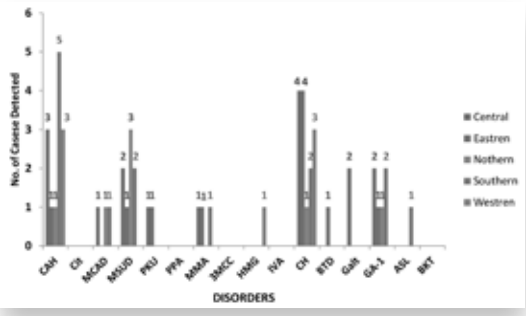

Figure 3: Number of abnormal cases detected in different regions of KSA in 2015.

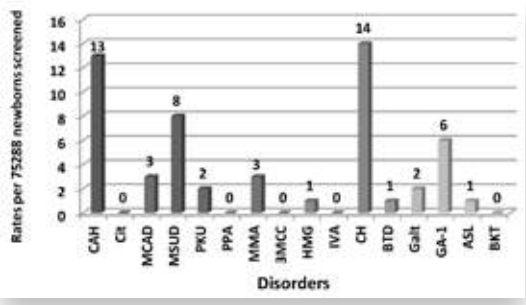

Figure 4: Number of cases per disorder detected in 2015.

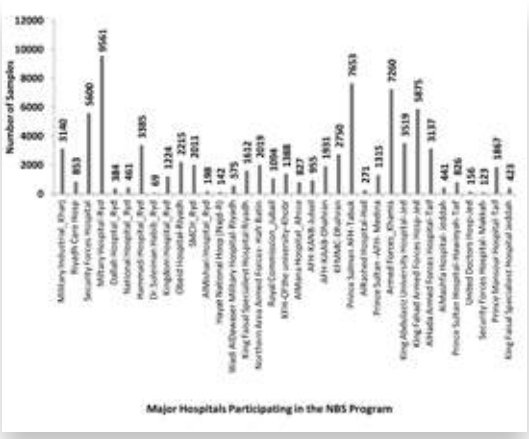

Figure 5: Number of samples received from major participating hospitals in 2015.

FUTURE DIRECTION

At NSBGL, we will continue to invest in & evaluate new technologies and techniques which aim at improving & expanding newborn screening for genetic disorders in Saudi Arabia. Examples include newborn screening for SCIDS (using qPCR) as well newborn screening for cystic fibrosis. In addition, we are developing comprehensive targeted as well as untargeted metabolomic assays which may be useful in clinical diagnosis of metabolic diseases as well as in biomarker discovery for metabolic and non-metabolic disorders which may be of therapeutic, prognostic value.

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regimens in Pompe disease. *Neuromuscul Disord*. 2015 Apr;25(4):321-32.

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NATIONAL & INTERNATIONAL PRESNETATIONS:

- Majed Dasouki. Newborn Screening for Severe Combined Immune Deficiency Syndromes (SCIDS). The 10th Annual Pediatric Review Conference (10th APRC), Amman, Jordan, February 26 -27, 2015.
- Majed Dasouki. Development and application of a gene panel for investigation of Dysmorphia/ Dysplasia. ThermoFisher Scientific Workshop, Arab Health, 27th January 2015. Dubai, UAE.
- Majed Dasouki. What is Massively Parallel/Next Generation Sequencing & What is Its Value for the Pediatrician? The 10th Annual Pediatric Review Conference (10th APRC). Amman, Jordan, February 26 -27, 2015.
- Majed Dasouki. The Saudi Mendeliome Experience. "The 15th International Conference of Jordan Pediatric Society and the 20th Congress Union & Arab Pediatric Societies". 29 April–2 May, 2015. Amman, Jordan.
- Majed Dasouki. Hereditary (Familial) Cancers in Children. "The 15th International Conference of Jordan Pediatric Society and the 20th Congress Union & Arab Pediatric Societies". 29 April–2 May, 2015. Amman, Jordan.
- Majed Dasouki. The Clinical Utility of a Proton Ion Ampliseq Based Inborn Errors of Metabolism Gene Panel. "PERSONALIZEDMEDICINECONFERENCE 2015: From the Genome to Precision Medicine, KFSH&RC Vision 20/20". 5–6 May 2015. KFSHRC. Riyadh, Saudi Arabia.

- Majed Dasouki. Ion AmpliSeq-based gene research panels—the Saudi Mendeliome Group experience. Thermo Fisher Scientific lunch seminar. ASHG annual meeting. October 7, 2015. Baltimore, MD, USA.
- Fahad ELBadawi. Educational training on Newborn Screening. United Doctors Hospital, Jeddah. May 27 & 28, 2015.

SAUDI DIAGNOSTICS LABORATORY

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Brian F. Meyer, PhD

MEMBERS
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SAUDI DIAGNOSTICS LABORATORY (SDL) APPLIES THE translational Research Programs of the Department of Genetics for the provision of molecular diagnostic services for patient care. During 2015, SDL continued to grow in the areas of diagnostics for inherited diseases, prenatal testing and carrier screening. SDL over several years has built a substantial database of samples and clinically validated results that are now, together with initiatives of the Saudi Human Genome Program (SHGP), proving to be very useful for the development and validation of new diagnostic and screening tests.

SDL performs a repertoire of over 200 tests many of which are unique to its operation. Through these activities the KFSHRC is becoming increasingly independent in molecular genetic testing. Animal genetics is a significant component of services offered by SDL. This is now a mature service dealing with an excess of 2500 samples per year for parentage verification and registration of Arabian horses. SDL is fully recognized for this purpose by the World Arabian Horse Organization (WAHO) and is a member of the International Society for Animal Genetics.

SDL provides diagnostic services for many clinical departments and sections at the KFSHRC. These include Medical Genetics, Pediatrics, Neurosciences, Obstetrics and Gynecology, Pediatric Immunology and Pediatric Nephrology among others. During 2015 over 2500 diagnostic tests were performed by SDL in support of these services. Preventative medicine through carrier detection and prenatal testing is a major service activity of SDL. Prenatal testing is a regular part of the SDL workflow with over 300 cases having been processed in 2015. SDL is working closely with the Research laboratories of the Department of Genetics and the SHGP to advance capabilities in prenatal testing. During 2012 SDL worked closely with research sections in the Department of Genetics and the SHGP to build a capacity for diagnostic implementation of Next Generation Sequencing. It is anticipated that in 2016 this will result in a major expansion of molecular testing based upon the introduction of gene panels and whole exome sequencing.

SEQUENCING CORE FACILITY

HEAD
Dorota Monies, PhD

MEMBERS
Muna Al Breacan, BSc
Faisal Bin Humaid, BSc
Sara Al Haibey, BSc
Dyala Jaroudi, MSc
Ewa Naim, MPharm

THE DNA SEQUENCING FACILITY USES STATE-OF-THE-ART technology and methodology to produce high quality DNA sequences in a time span of 2-3 business days. DNA samples are sequenced using BigDye Terminator chemistry and resolved on the ABI 3730xl DNA Analyzer. BigDye Terminator chemistry utilizes ddNTPs that are labeled with a fluorescent dye specific for each nucleotide, allowing sequencing in one reaction tube. All sequencing reactions are set up robotically using Beckman Automated Workstation (Biomek NX) and cycled on a high capacity thermal cyclers (ABI 2720). The sequences are then run on the ABI 3730xl DNA Analyzers (5 instruemnts). The ABI 3730xl uses a capillary electrophoresis system that creates a sensitive detection system, long sequence reads (up to a 1000 bases for high quality DNA), short run times, and low operating/reagent costs. The ABI 3730xl DNA Analyzer is an automated system (sample loading, separation matrix preparation, and sequence analysis) which coupled with the facility's liquid handling robot, dramatically reduces the introduction of human error.

SERVICES OFFERED

DNA PURIFICATION

The Core uses the Agencourt AMPure and CleanSEQ system which utilizes Solid-Phase Paramagnetic Bead technology: AMPure utilizes an optimized buffer to selectively bind PCR amplicons (100bp and larger) to paramagnetic beads. Excess oligos, salts and enzymes is removed using a simple washing procedure. CleanSEQ efficiently purifies sequencing products

DNA SEQUENCING

All DNA samples are sequenced using BigDye Terminator chemistry with universal M13 forward and reverse primers or user-supplied primers. The DNA sequencing reactions are electrophoresed on ABI's 3730xl DNA Analyzers which can produce read lengths of 1000 bases for high quality DNA templates. All sequencing reaction plates and individual samples must have acceptable quality controls before the results are released. The DNA Sequencing Facility employs both objective and subjective quality controls. All samples have to be submitted to the laboratory according to the Sequencing Core Facility Requirements. For each sequencing reaction plate, all negative controls must be negative and the positive controls must pass certain quality criteria before sequences are released to each investigator.

FRAGMENT ANALYSIS

The DNA Sequencing Facility also provides a DNA fragment analysis service. The fragment analysis service is used for microsatellite genotyping, SNP genotyping and mutation detection. The DNA Sequencing Facility performs high throughput analysis of microsatellite markers using the Applied Biosystems 3730xl platforms for rapid turnaround time and highly accurate allele scoring. This instrumentation can perform multiplex analysis of several markers per capillary. In a single capillary, markers of multiple base sizes can be electrophoresed together. Up to four fluorescent dyes (FAM, VIC, PET, and NED) can be used in the same PCR reaction, enabling several microsatellites to be studied in a single run.

RESEARCH PROJECTS/ACTIVITIES

The Unit is involved in a broad range of medical scientific and diagnostic work, contributing to most of the research projects carried out in the Department of Genetics. Core cooperates with 85 researches within the Research Center.

PROJECT TITLE: Molecular Genetic Characterization of Hereditary Gastrointestinal Diseases
RAC # 2080016

INVESTIGATORS: *Rahbeeni Z, Monies D, Al-Zaidan H, Mehaidib A, Al-Edreesi M, Faqih, M, Meyer B*

PROJECT DESCRIPTION: Molecular genetic charkterization of HGD in the Saudi population will shed new light on the pathogenesis of these rare disorders. Identification of underlying genes and associated mutations are critical for counseling of patients, their families and for preventative and management strategies.

PROJECT PROGRESS: We described the molecular genetic basis of Tricho-hepatoenteric syndrome (THES) in Arabs patients with novel mutations of SKIV2L (c.3559_3579del, p.1187_1193del) and TTC37 (C4102T, p.Q1368X). Interestingly the congenital presence of caféau-lait spots and their distribution in the pelvis and lower limbs were a unique and consistent clinical feature of these patients that may aid differential diagnosis of Chronic Diarrheal Disorders. This study expands allelic and phenotypic heterogeneity of SD/THES.

PROJECT TITLE: The Molecular Basis of Inherited Reproductive Disorders
RAC#2091054

INVESTIGATORS: *Al Tassan N, Meyer B, Alkuraya F, Wakil S, Monies D, Crowley W*

PROJECT DESCRIPTION: This approved study in collaboration with Reproductive Endocrine Unit, Massachusetts General Hospital, Boston, USA, aims to identify genes that control puberty and reproduction in humans and characterize the phenotypic spectrum of patients with these genetic defects.

PROJECT PROGRESS: The sequencing of 1200 patients for 16 genes was completed; a number of novel and previously reported mutations were identified. Functional assessment of mutations is ongoing. The effect of digeneic mutation was ascertained in zebra fish.

PROJECT TITLE: Autozygome Sequencing for High Throughput Identification of Genes with Biallelic Inactivation in Healthy Humans: Understanding Genetic Influence on Human Phenotypic Variation -The Human Knockout Project
RAC#2140 016

INVESTIGATORS: *Alkuraya F, Monies D, Alkhenaizan A, Abouelhoda M*

PROJECT DESCRIPTION: Understanding the role of genes in health and disease states is the essence of human genetics research. We are interested in the phenotypic variation among healthy individuals that results from complete loss of function of certain genes because these are likely to exert a large effect size that is easier to detect. Since the autozygous intervals in the genome (autozygome) that result from consanguinity have been shown to enrich for the occurrence of biallelic loss of function, we propose to perform whole-exome sequencing of 10,000 healthy Saudis whose parents are at least first-cousins in their degree of relatedness. We hope the resulting catalogue of "knockouts" among healthy individuals will provide a valuable shortcut to the understanding of genetic contribution to subtle phenotypes that are very difficult to study otherwise.

PROJECT PROGRESS: Ongoing, enrolling Saudi individuals and collecting sample.

KACST FUNDED PROJECTS

PROJECT TITLE: The Patholgy and Genetics of Limb-Girdle Muscular Dystrophy in Saudi Arabia
KACST # 2070 005

INVESTIGATORS: *Bohlega S, Monies D, Meyer B, Wakil S, Alazami A, Al Muhaizea M, Al Hindi H, Al Hamoud I*

PROJECT PROGRESS: To date, 50 families were enrolled. Neuro Gene Panel (NGS) was used for molecular diagnosis. We found a DNA mutation responsible for LGMD in 44 (88%) patients. In 7 (6%) families the Neuro Panel didn't reveal any pathogenic mutation and these subjects individuals are subjected for the Whole Exome Sequencing which revealed several novel genes.

PROJECT TITLE: The Molecular Basis of ADHD in Saudi Arabia
RAC # 2120001
(NCPST KACST Project 12-BIO2346-20

INVESTIGATORS: *Al Tassan N, Ghaziuddin M, Monies D, Wakil S, Meyer B, Abebe D.*

PROJECT PROGRESS: Homozygosity mapping and linkage analysis in AR families with 2 or 3 affected individuals identified novel loci, candidate gene screening is ongoing. Exome Sequencing of Trio's is ongoing in the Saudi Human Genome Program Lab.

PROJECT TITLE: Genetic Basis of Mental Retardation
RAC # 2080 036
KACST Project No 08-MED499-20

INVESTIGATORS: *Meyer B, Kaya N, Monies D, Al-Owain M, Al-Sayed M, Al-Hassnan Z, Bohlega S, Dalaan H, Al-Yamani S, Al-Semari A*

PROJECT PROGRESS: To date we recruited 45 families and linkage analysis was performed for all the families with more than one affected individual. Patients' samples are currently processed with Neuro Gene Panel (NGS) and Whole-Exome sequencing.

PROJECT TITLE: Use of Cell Free Fetal DNA for Non-Invasive Prenatal Diagnosis of Inherited Diseases and Aneuploids
KACST # 2140 012

INVESTIGATORS: *Meyer B., Imitiaz F., Monies D., Wakil S., Wesam K.*

PROJECT PROGRESS: Since RAC approval and informed consent for this project was approved (21 July 2014), efforts have been made to collect whole blood samples for plasma isolation from 69 pregnant mothers who were undergoing prenatal molecular genetic testing at KFSH&RC. Cell free fetal DNA will be isolated and will be used for establishment of RHD typing. In parallel, SNP analysis has been performed on 23 consented mothers and their unborn babies.

RESEARCH PUBLICATIONS

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- Clinical and pathological heterogeneity of a congenital disorder of glycosylation manifesting as a myasthenic/myopathic syndrome. Monies DM, Al-Hindi HN, Al-Muhaizea MA, Jaroudi DJ, Al-Younes B, Naim EA, Wakil SM, Meyer BF, Bohlega S. *Neuromuscul Disord*. 2014 Apr; 24 (4):353-9.
- Functionally compromised CHD7 alleles in patients with isolated GnRH deficiency. Balasubramanian R, Choi JH, Francescatto L, Willer J, Horton ER, Asimacopoulos EP, Stankovic KM, Plummer L, Buck CL, Quinton R, Nebesio TD, Mericq V, Merino PM, Meyer BF, Monies D, Gusella JF, Al Tassan N, Katsanis N, Crowley WF Jr. *Proc Natl Acad Sci U S A*. 2014 Dec 16;111(50):17953-8.
- Association of a mutation in LACC1 with a monogenic form of systemic juvenile idiopathic arthritis. Wakil SM, Monies DM, Abouelhoda M, Al-Tassan N, Al-Dusery H, Naim EA, Al-Younes B, Shinwari J, Al-Mohanna FA, Meyer BF, Al-Mayouf S. *Arthritis Rheumatol*. 2015 Jan;67(1):288-95.
- Accelerating novel candidate gene discovery in neurogenetic disorders via whole-exome sequencing of prescreened multiplex consanguineous families. Alazami AM, Patel N, Shamseldin HE, Anazi S, Al-Dosari MS, Alzahrani F, Hijazi H, Alshammari M, Aldahmesh MA, Salih MA, Faqeih E, Alhashem A, Bashiri FA, Al-Owain M, Kentab AY, Sogaty S, Al Tala S, Temsah MH, Tulbah M, Aljelaify RF, Alshahwan SA, Seidahmed MZ, Alhadid AA, Aldhalaan H, AlQallaf F, Kurdi W, Alfadhel M, Babay Z, Alsogheer M, Kaya N, Al-Hassnan ZN, Abdel-Salam GM, Al-Sannaa N, Al Mutairi F, El Khashab HY, Bohlega S, Jia X, Nguyen HC, Hammami R, Adly N, Mohamed JY, Abdulwahab F, Ibrahim N, Naim EA, Al-Younes B, Meyer BF, Hashem M, Shaheen R, Xiong Y, Abouelhoda M, Aldeeri AA, Monies DM, Alkuraya FS. *Cell Rep*. 2015 Jan 13;10(2):148-61
- Expanding phenotypic and allelic heterogeneity of tricho-hepato-enteric syndrome. Monies DM, Rahbeeni Z, Abouelhoda M, Naim EA, Al-

Younes B, Meyer BF, Al-Mehaidib A. *J Pediatr Gastroenterol Nutr*. 2015 Mar;60(3):352-6.

- Clinical and genetic features of anoctaminopathy in Saudi Arabia. Bohlega S, Monies DM, Abulaban AA, Murad HN, Alhindi HN, Meyer BF. Neurosciences (Riyadh). 2015 Apr;20(2):173-7.
- Comprehensive gene panels provide advantages over clinical exome sequencing for Mendelian diseases. Saudi Mendeliome Group. *Genome Biol*. 2015 Jun 26;16:134.
- Identification of a novel MKS locus defined by TMEM107 mutation. Shaheen R, Almoisheer A, Faqeih E, Babay Z, Monies D, Tassan N, Abouelhoda M, Kurdi W, Al Mardawi E, Khalil MM, Seidahmed MZ, Alnemer M, Alsahan N, Sogaty S, Alhashem A, Singh A, Goyal M, Kapoor S, Alomar R, Ibrahim N, Alkuraya FS. *Hum Mol Genet*. 2015 Sep 15;24(18):5211-8.
- Expanding the clinical, allelic, and locus heterogeneity of retinal dystrophies. Patel N, Aldahmesh MA, Alkuraya H, Anazi S, Alsharif H, Khan AO, Sunker A, Al-Mohsen S, Abboud EB, Nowilaty SR, Alowain M, Al-Zaidan H, Al-Saud B, Alasmari A, Abdel-Salam GM, Abouelhoda M, Abdulwahab FM, Ibrahim N, Naim E, Al-Younes B, E AlMostafa A, AlIssa A, Hashem M, Buzovetsky O, Xiong Y, Monies D, Altassan N, Shaheen R, Al-Hazzaa SA, Alkuraya FS.,*Genet Med*. 2015 Sep 10.
- Exome-based case-control association study using extreme phenotype design reveals novel candidates with protective effect in diabetic retinopathy. Shtir C, Aldahmesh MA, Al-Dahmash S, Abboud E, Alkuraya H, Abouammoh MA, Nowailaty SR, Al-Thubaiti G, Naim EA, ALYounes B, Binhumaid FS, ALOtaibi AB, Altamimi AS, Alamer FH, Hashem M, Abouelhoda M, Monies D, Alkuraya FS. *Hum Genet*. 2015 Dec 22.
- KIAA0556 is a novel ciliary basal body component mutated in Joubert syndrome. Sanders AA, de Vrieze E, Alazami AM, Alzahrani F, Malarkey EB, Sorusch N, Tebbe L, Kuhns S, van Dam TJ, Alhashem A, Tabarki B, Lu Q, Lambacher NJ, Kennedy JE, Bowie RV, Hetterschijt L, van Beersum S, van Reeuwijk J, Boldt K, Kremer H, Kesterson RA, Monies D, Abouelhoda M, Roepman R, Huynen MH, Ueffing M, Russell RB, Wolfrum U, Yoder BK, van Wijk E, Alkuraya FS, Blacque OE. *Genome Biol*. 2015 Dec 29;16(1):293

HUMAN CANCER GENOMIC RESEARCH

HUMAN CANCER GENOMIC RESEARCH

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MISSION

The main goal of Human Cancer Genomic Research (HCGR) laboratory has been to identify dysregulation in various genes and signaling pathways in those cancer that are more prevalent in the Kingdom of Saudi Arabia. The researchers at HCGR are continuing their research in pursuing these challenges by performing translational studies to identify molecular and genetic variations that may be playing a role in the pathogenesis of these cancers. Once these molecular and genetic variations are identified, intensive data analysis using clinical history is done to determine the role of these alterations in the pathogenesis of cancers. Targeting these identified molecular and genetic alterations using either molecular inhibitors, small interference RNA (siRNA) or antibodies are also performed to identify genes that can be therapeutically targeted for the improvement of cancer therapy for these cancers. HCGR is equipped with state of the art technology that is routinely used to perform high quality translational research. These state of the art equipment used include the HiSeq illumina sequencer, affymetrix, tissue micro arrayer and high throughput sequencing analyzer. Therefore, the main mission of HCGR is to design better strategies to diagnose, prognosticate and treat neoplasm that are specifically relevant to Saudi Arabian as compared to the Western population.

Human Cancer Genomic Research Program is devoted to perform high quality research according to international standards. Its centerpiece is a unique biorepository centre consisting of archival frozen tumor tissue samples, DNA and human cancer cell lines that have been either procured from ATCC as well as in house established cell lines that allow large scale and high throughput research. Our long-term goal is towards developing diagnostic or therapeutic strategies to improve the management of cancer in the Kingdom of Saudi Arabia and provide unprecedented tools for translational research in the region.

EXPERIMENTAL MOLECULAR PATHOLOGY

In 2015, we have continued our research towards identifying genetic alterations in cancers that are more prevalent in the Kingdom of Saudi Arabia. Extensive studies have been conducted on papillary thyroid cancer, colorectal cancer, epithelial ovarian cancer and breast cancer. Identification of dysregulated survival pathways are sought that maybe playing a role in the pathogenesis of these cancers. Once these pathways are identified, they are further targeted using specific molecular inhibitors as well as siRNA to determine whether therapeutic intervention can lead to better response to therapy when given in conjunction with chemotherapeutic drugs. Finally, over-expression of mTOR, XIAP and FoxM1 has also been identified in breast, thyroid and ovarian cancer samples and further investigation and experimentation is ongoing to elicit the role of these genes in cancer pathology.

MOLECULAR ONCOLOGY

This department focuses mainly on translational studies, towards developing diagnosis or therapeutic strategies in improving the management of cancer. This is a unique facility and provides unprecedented tools for translational research in the region.

Taking a cue from the findings of the unit of experimental molecular pathology, in 2015, we have now used mTOR as a molecular target as they have been found to be dysregulated in EOC. Dysregulation of mTOR signaling complex

has been studied in detail in EOC samples and in these studies, we were able to target mTOR activity using either pharmacological inhibitor such as Torin2 or siRNA knockdown strategies to inhibit cell growth and induce apoptosis in EOC cell lines. Finally, we synergistically treated EOC cells with combination of mTOR inhibitor; Torin2 and chemotherapeutic agent; cisplatin to induce apoptosis and inhibit cell viability *in vitro* and regress EOC xenografts *in vivo*. These results may pave the way for newer and more efficient treatment for these aggressive cancers.

Another protein that has been found to be over-expressed in breast cancer is Poly (ADP) Ribose Polymerase (PARP) that is involved in single stranded DNA repair. Over-expression of PARP has been shown to increase the aggressiveness of breast cancer and induces a poor prognosis. Currently, we are targeting over-expression of PARP using either PARP inhibitor; Olaparib alone or in combination of with other molecular inhibitors for efficient apoptosis to determine whether targeting PARP maybe beneficial for the management of breast cancer.

BIOLOGICAL REPOSITORY CENTRE

The Biological repository Centre (BRC) located at the KFNCCC research centre is a state of the art facility where proper preservation & storage of archival frozen tumor and normal tissue samples is done in a timely and systematic manner. Multiple storage equipment including cryo-preservation in Liquid Nitrogen, -80oC and -20oC freezers are used for storage purposes. These equipment are consistently monitored 24 hours so that the integrity and quality of the samples are not compromised. DNA and RNA extracted from these frozen samples are being utilized for mutational analysis and differential expression studies in various projects. Following are the various tasks that were accomplished during 2015.

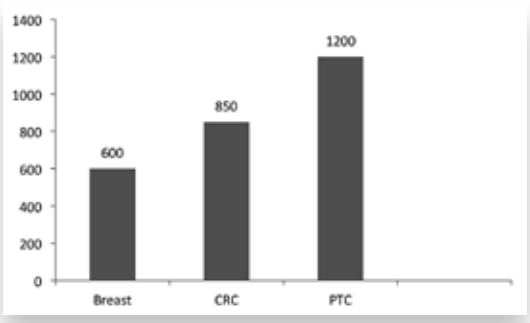
TASKS

Collect and maintain archives of frozen tissues (normal and neoplastic), serum, paraffin blocks and commercial cell lines.

ACTIVITIES

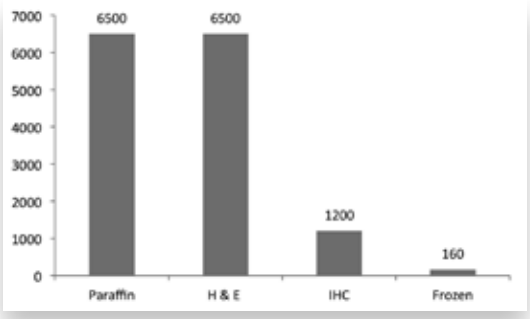
BRC is handling a number of different projects in which biological samples are being optimally stored and further processing is being done as and when requested by the researchers.

1. Processing biomaterial (DNA and/or RNA extraction from TMA punches of paraffin blocks) for various research projects – a total of 2650 specimens were processed in the year 2014-2015. Five to ten DNA punches obtained for each tumor specimen.
2. Cell blocks prepared from 50 cell lines used for immunohistochemistry
3. Commercial cell lines acquired from ATCC and other biorepository centers expanded and grown in bulk over 500 vials frozen and stored in liquid nitrogen.
4. Processing of fresh tissue for frozen sections and formalin fixed paraffin embedded (FFPE) tissues from archival paraffin blocks for routine H&E staining and immunohistochemistry. This may include fixation, paraffin embedding, tissue cutting and section staining. Sections are cut and stained for all routine histochemical staining including hematoxylin and eosin.



DNA punches

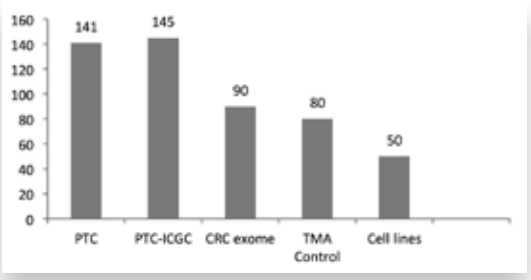
6. Storing biomaterial under controlled temperature:
   - Storage of various commercial cell lines which are being used for various ongoing research projects in our department
   - Maintaining supply of liquid nitrogen for cryomed freezers for department of genetics, Research Centre
7. Maintaining and distributing commercially available cell lines (ATCC) to the research investigator/clinicians with RAC approved projects.



Number of sections of histology

TISSUE MICROARRAY (TMA) UNIT

Human Cancer Genomics Research has established TMA technology and has an extensive archival of tumor specimens in a TMA format. A total of 506 tumor and normal tissue specimens were arrayed in a TMA format in year 2014-2015. Six to ten TMA replicas obtained for each tumor specimens. In addition we have 2 cell line block TMA.



Tissue microarray construction

GRANTS

PROJECT TITLE: The role of FoxM1 in Saudi Arabian Ovarian Cancer: Grant funded project by National Science, Technology Innovation Plan (NSTIP)
RAC# 2140 033 (NSTIP 10-BIO963-20)

Ovarian cancer (EOC) is the most lethal gynaecologic malignancies and this is due in large part to the resistance of recurrent ovarian cancer cells to standard chemotherapeutic strategies. Resistance to apoptotic cell death is a fundamental characteristic of cancer cells, and a primary cause of treatment failure. Many of the ovarian cancer cells are resistant to the conventional therapeutic agents. This resistance to chemotherapy results in its recurrence and ultimately the loss of life. Therefore identification of new therapeutic strategies for treatment of ovarian cancer is necessary.

Forkhead Box M1 (FoxM1). FoxM1 is a transcription factor that regulates the expression of a number of genes that are involved in cell cycle regulation and metastasis. Over-expression of FoxM1 has been shown in a variety of cancer however its role has not been fully elucidated in epithelial ovarian cancers (EOC). We have obtained preliminary data that FoxM1 is over-expressed in 47.4% Saudi EOC and significantly associated with proliferative marker Ki67 ($p<0.0001$). Therefore we hypothesize that FoxM1 mediated pathway plays a critical role in the pathogenesis of Saudi EOC via promoting cell proliferation and metastasis and have potentials for therapeutic intervention for the treatment of these cancers. We will investigate the role of FoxM1signaling pathway in EOC using a large tissue microarray cohort of tumor samples, a panel of EOC cell lines, pharmacological inhibitor, FoxM1 over-expressing system, gene silencing by siRNA and nude mouse model. Our specific aim is (1) to determine whether expression of FoxM1 in Saudi EOC is associated with genes involved in cell cycle regulation, apoptosis, invasion and migration as well as clinical parameters and prognosis. The specific aim is (2) to determine whether down-regulation of FoxM1 induces cell cycle arrest and apoptosis in EOC cell lines. In aim (3) we will attempt to identify the molecular mechanism by which FoxM1 over-expression regulates invasion and angiogenesis in EOC cells with a particular focus on how FoxM1 expression regulates the expression of MMP2, MMP9 and VEGF genes. The aim (4) will determine the effect of FoxM1 overexpression in EOC tumorigenesis in nude mouse model.

The outcome of this study will provide a better understanding of EOC and should have important clinical implications, as it could result in the development of new and better strategies for targeted therapeutic intervention for the treatment of Saudi Arabian EOC tumours.

In this regard, we examined in detail, a survival pathway that is associated with FoxM1 expression; mTOR survival pathway and we had the following findings:

Mammalian target of rapamycin (mTOR) and Phosphatidylinositol 3-kinase (PI3K) are two key components of PI3K/Akt/mTOR signaling pathway. Dysregulation of these pathways have been found in many cancers including epithelial ovarian cancer (EOC), however, the role of mTOR has not been fully elucidated in Middle Eastern EOC. Therefore, we investigated the activation of mTOR complexes (mTORC1 and mTORC2) in a cohort of 156 EOC from Saudi Arabia by immunohistochemistry in a tissue microarray format. mTORC1 and mTORC2 were found to be activated in 55/156 (37.7%) and 63/140 (45%) of EOC samples respectively. mTORC1 was significantly associated with mTORC2 ($p<0.0001$) activation and both mTOR complexes were significantly associated with p-AKT ($p=0.0205$ and 0.0298) and p-P70S6 ($p<0.0001$ and 0.0035) respectively. Interestingly, mTOR activation incurred a poor progression free survival ($p=0.0188$) in EOC. Next, *in vitro* effect of inactivation of mTOR complexes was evaluated using a second generation mTOR inhibitor; Torin2 on a panel of EOC cell lines. Torin2 treatment decreased cell viability and induced apoptosis in dose dependent manner via inactivation of mTORC1 and mTORC2 and their downstream targets in EOC cell lines. Furthermore, treatment of EOC cells with sub-toxic dose of Torin2 potentiated cisplatin induced apoptotic response in EOC cell lines. Finally, we studied the *in vivo* effect of combination of Torin2 and cisplatin and found that this combination synergistically inhibited tumor growth in nude mice. These studies highlight the importance of targeting mTOR survival pathway and suggest that co-treatment with cisplatin and Torin2 may be beneficial for the management of EOC.

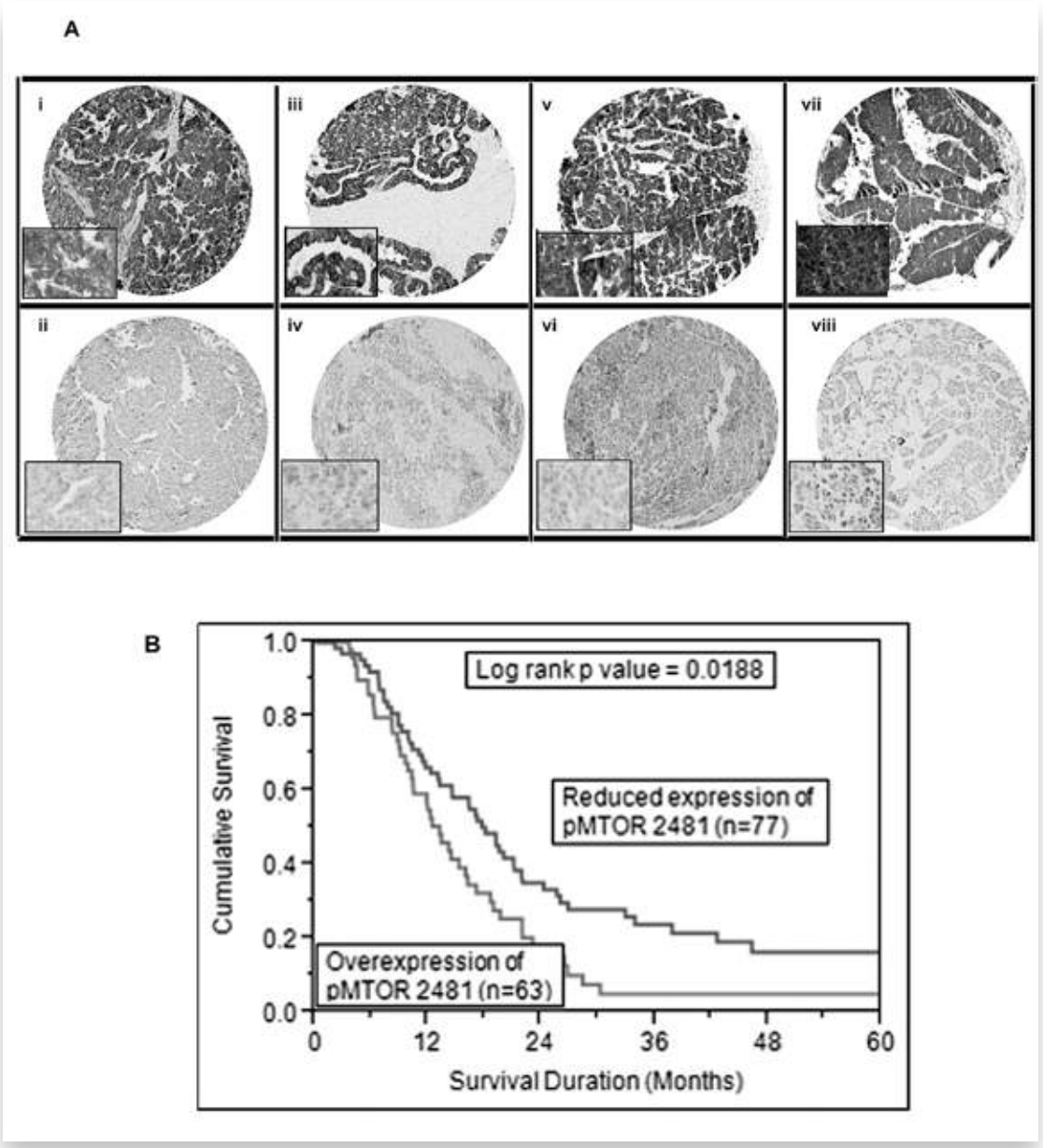


Figure 1. **(A)** Immunohistochemical analysis of p-mTORSer2481, p-mTOR Ser2448, p-AKT and p-4EBP1 expression in Epithelial Ovarian Carcinoma. TMA spots showing overexpression of **(i)** p-mTOR (ser2481), **(iii)** p-mTOR (Ser2448), **(v)** p-AKT and **(vii)** p-4EBP1. In contrast, different TMA spots showing reduced/absent expression of **(ii)** p-mTOR (Ser2481), **(iv)** p-mTOR (Ser2448), **(vi)** p-AKT and **(viii)** p-4EBP1. 20x magnification on Olympus BX-51 microscope (Olympus America, Center Valley, PA, USA) with inset showing 40 x magnifications of the same TMA spot. **(B)** Kaplan Meier survival curve in EOC patients showing poor survival in p-mTOR Ser2481 overexpressed cases compared to those with reduced expression (p=0.0188).

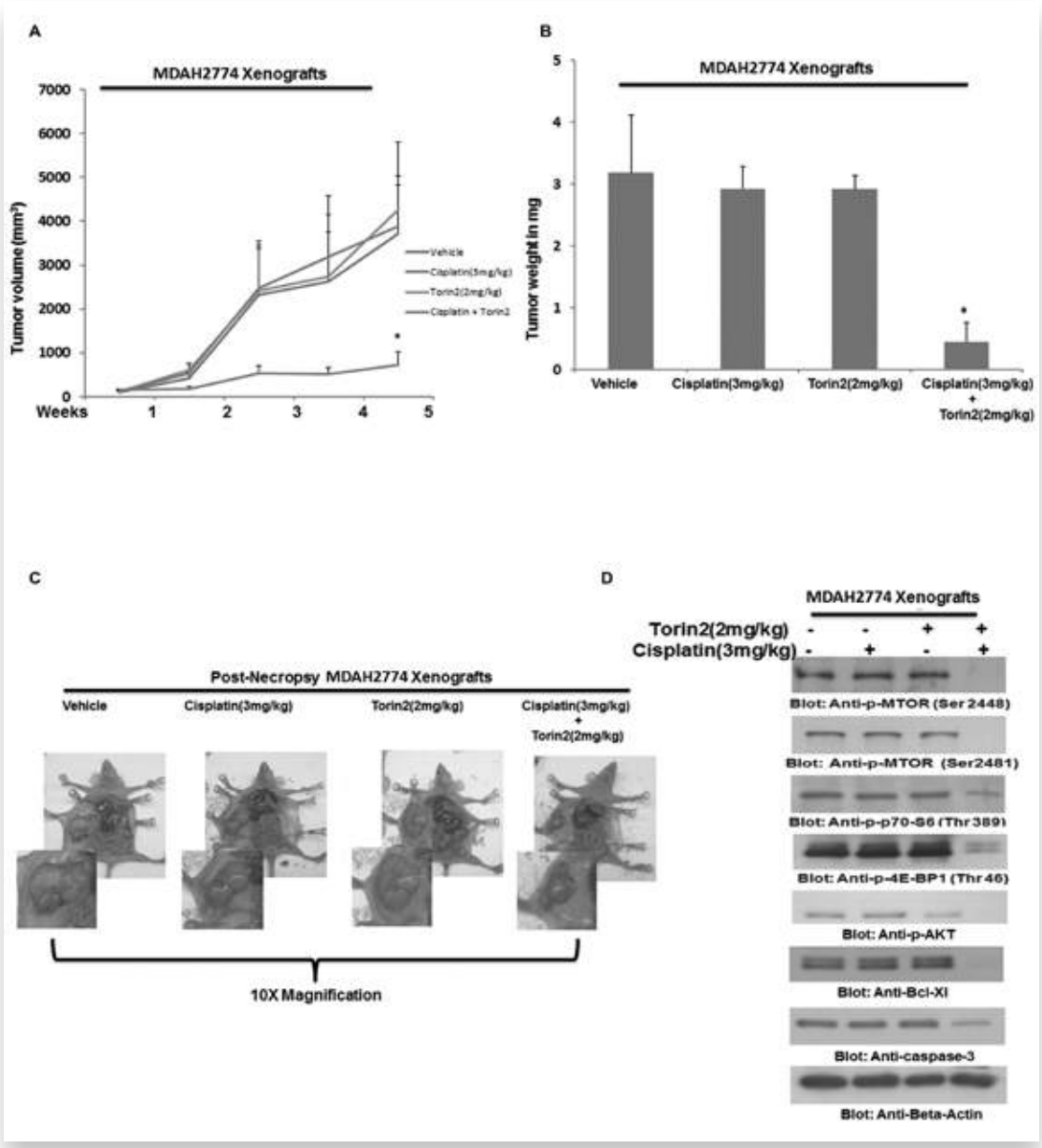


Figure 2. Inhibition of EOC-cell tumor xenografts growth by co-treatment with Torin2 and cisplatin. Nude female mice at 6 weeks of age were injected subcutaneously with ten million MDAH2774 cells. After one week, the animals were divided into 4 groups, the first group received DMSO (vehicle) alone while the other three groups received Torin2 (2mg/kg), cisplatin (3mg/kg) and combination of both, injected twice weekly, intra-peritoneally. After 5 weeks treatment, mice were sacrificed and tumors were collected. **(A)** The volume of each tumor was measured every week. The average (n = 5) tumor volume in each group of mice was calculated, * $p < 0.05$ statistical significance. **(B)** After 5 weeks treatment, mice were sacrificed and mean tumor weight (±SD) was calculated in each group. * $p < 0.05$ statistical significance. **(C)** Representative tumor images of each group of mice after necropsy. Inset picture showing 10X magnification. **(D)** Whole-xenograft homogenates from mice injected with MDAH2774 cells were immuno-blotted with antibodies against p-mTOR Ser2448, p-mTOR Ser2481, p-P70S6, p-4E-BP1, p-AKT, Bcl-XI, caspase 3 and Beta-actin.

PROJECT TITLE: Role of XIAP in Pathogenesis of Saudi Arabian Papillary Thyroid Carcinoma. Grant funded project by National Science, Technology and Innovation Plan (NSTIP)

RAC 2140 010 (NSTIP 11-BIO2219-20)

In this project, we have attempted to identify XIAP as a therapeutic target for the treatment option in a subset of PTC using either specific inhibitor; Embelin alone or in combination with PI3-kinase/AKT inhibitor; LY294002. The summary of the results are as follows: Papillary thyroid cancer (PTC) is the second most common cancer in females in Saudi Arabia. However, the pathogenesis of PTC is still not fully elucidated. In order to identify potential genes that play important role in progression of PTC, we studied the role of XIAP as a potential prognostic marker and therapeutic target in a large cohort of PTC samples and cell lines. DNA microarray chip was used to screen for gene copy number. XIAP expression was assessed by immunohistochemistry in a tissue micro-array format on a cohort of 1022 clinical samples. *In vitro* and *in vivo* studies were performed using Embelin and/or LY294002 on PTC cell lines. XIAP was found to be amplified in 14/29 and over-expressed in 47.4% PTC cases. XIAP over-expression was significantly associated with old age, extra-thyroidal extension, tumor size, nodal involvement, tall-cell variant, advanced stage disease and significantly poor disease free survival ($p=0.0138$). XIAP was also significantly associated with p-AKT ($p<0.0001$), Bcl-Xl ($p<0.0001$) and Ki67 ($p=0.0015$) proteins. Embelin treatment caused growth inhibition and apoptosis in PTC cell lines and induced tumor regression in PTC xenograft in nude mice. Finally, combination of sub-optimal doses of Embelin and LY294002 induced a synergistic apoptotic response in PTC cells. Therefore, we conclude with the following findings that XIAP dysregulation in PTC confers an aggressive phenotype with poor outcome. *In vitro* and *in vivo* studies using XIAP inhibitor suggest that this sub-group of PTC with over-expression of XIAP can be therapeutically targeted either alone or in combination to induce efficient apoptosis in these cancers.

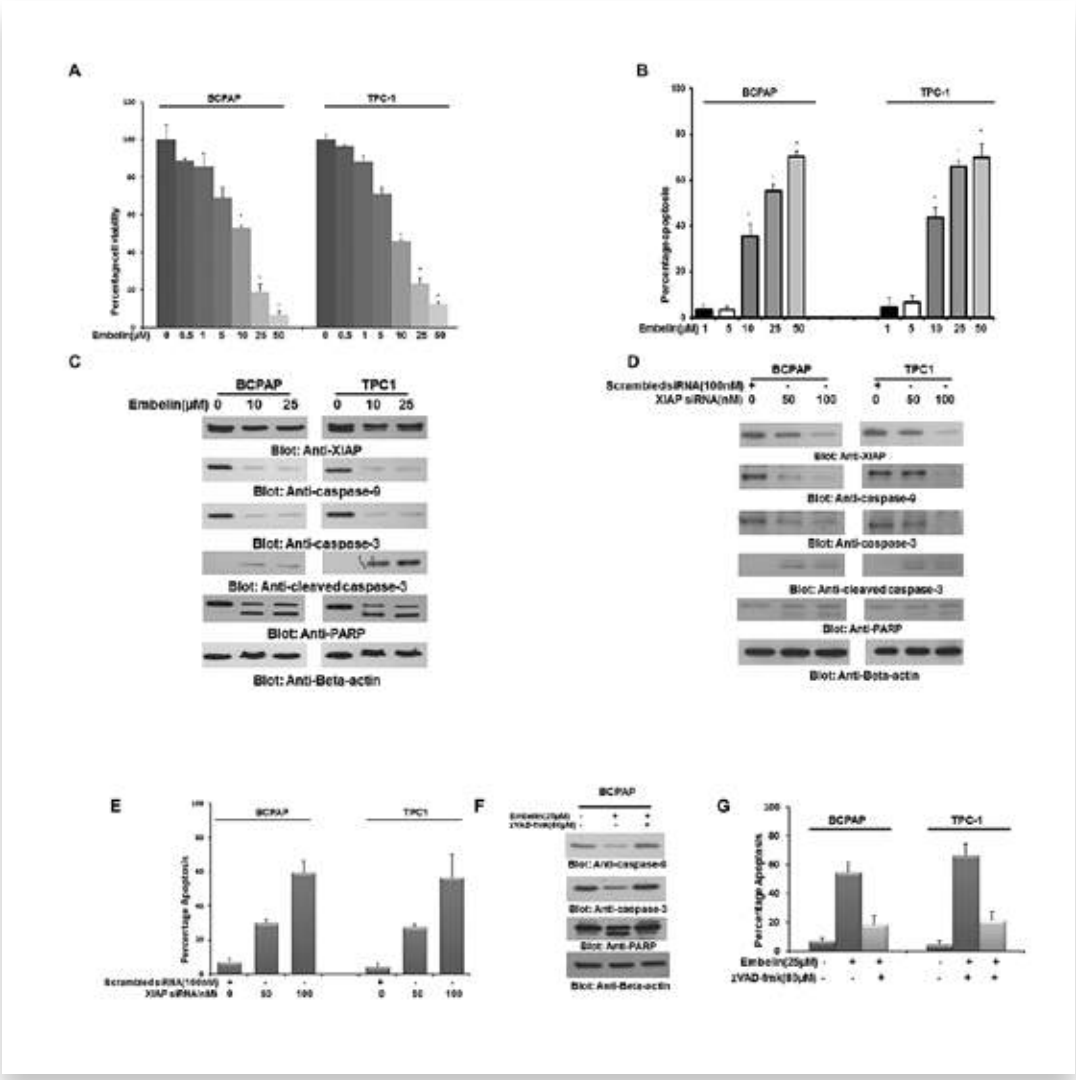


Figure 3. Embelin treatment inhibited cell viability and induced caspase dependent apoptosis in PTC cells. **(A)** PTC cell lines were incubated with 0-50μM Embelin for 24 hours. Cell viability was measured by MTT assays as described in Materials and Methods. The graph displays the mean +/- SD (standard deviation) of three independent experiments, * $p < 0.05$, statistically significant (Students t-test). **(B)** PTC cells were treated with 10 and 25μM Embelin (as indicated) for 24 hours and cells were subsequently stained with flourescein-conjugated annexin-V and propidium iodide (PI) and analyzed by flow cytometry. Bar graph denotes an average of three independent experiments. * $p < 0.05$, statistically significant (Students t-test). **(C)** BCPAP and TPC1 cells were treated with 10 and 25μM Embelin for 24 hours. Cells were lysed and equal amounts of proteins were separated by SDS-PAGE, transferred to PVDF membrane, and immunoblotted with antibodies against XIAP, caspase-9, caspase-3, cleaved caspase-3 and PARP. Beta-actin was used for equal loading. **(D)** BCPAP and TPC1 cells were treated with either scrambled siRNA or 50 and 100nM XIAP specific siRNA for 48 hours. Cells were lysed and equal amounts of proteins were separated by SDS-PAGE, transferred to PVDF membrane, and immunoblotted with antibodies against caspase-9, caspase-3, cleaved caspase-3 and PARP. Beta-actin was used for equal loading. **(E)** PTC cells were treated with either scrambled siRNA or 50 and 100nM specific siRNA against XIAP for 48 hours. Following treatment, cells were subsequently stained with flourescein-conjugated annexin-V and propidium iodide (PI) and analyzed by flow cytometry. Bar graph denotes an average of three independent experiments with standard deviation. (F and G) PTC cells were pre-treated with 80μM zVAD-fmk for 3 hours followed by treatment with 25μM Embelin for 24 hours. Following treatment, cells were either lysed and immunoblotted with antibodies against caspase-9, caspase-3, PARP and Beta-actin **(F)** or subsequently stained with flourescein-conjugated annexin-V and propidium iodide (PI) and analyzed by flow cytometry **(G)**. Bar graph denotes an average of three independent experiments with standard deviation

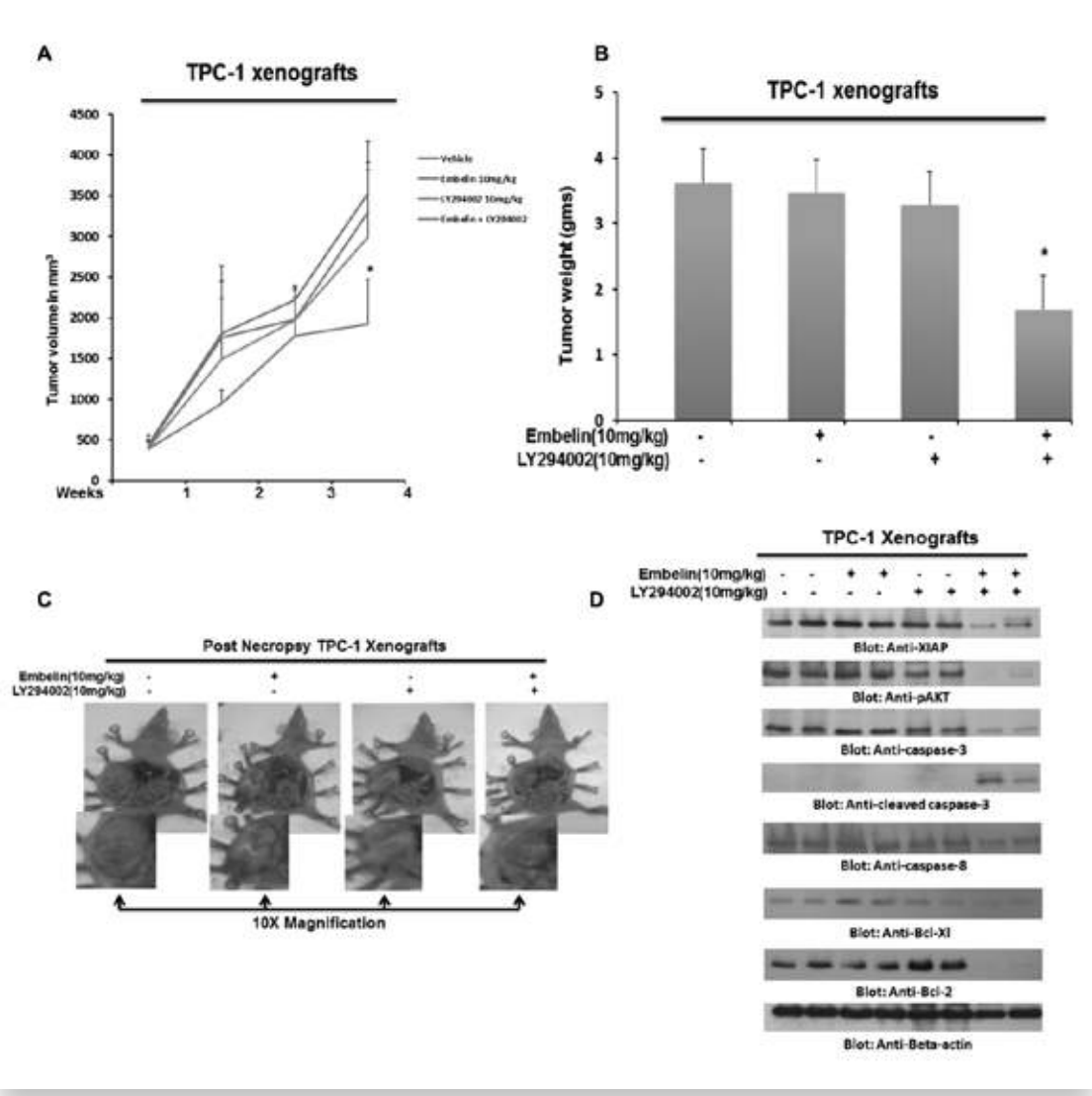


Figure 4. Inhibition of PTC-cell- tumor-xenografts growth by combination of Embelin and LY294002. Nude mice at 6 weeks of age were injected subcutaneously with ten million TPC1 cells. After one week, the animals were divided into four groups. **(A)** The volume of each tumor was measured every week. The average (n = 5) tumor volumes in vehicle-treated mice, mice treated with indicated doses of Embelin, LY294002 and a combination of Embelin and LY294002 were plotted. The results are expressed as mean ± SD (n = 5). *P <0.001 compared with vehicle-treated mice. **(B)** After 4 weeks treatment, mice were sacrificed and mean tumor weight (±SD) was calculated in each group. **(C)** Representative tumor images of each group of mice after necropsy. Inset showing 10Xmagnification. **(D)** Whole-cell homogenates from mice injected with TPC1cells were immuno-blotted with antibodies against XIAP, p-AKT, caspase 3, cleaved caspase 3, caspase-8, Bcl-XI, Bcl-2 and beta-actin.

PROJECT TITLE: Prognostic Significance of CARD10 in Saudi Colorectal Cancers. Grant funded project by National Science, Technology and Innovation Plan (NSTIP)
RAC# 2140 005 (NSTIP 10-BIO959-20)

In this KACST funded project, we have proposed to identify the prognostic importance of CARD10 and its associated molecular markers in the pathogenesis of colorectal carcinoma (CRC). During the last year, we were able to complete Fluorescent InSitu Hybridization (FISH) analysis on 770 CRC cases. We found that CARD10 was amplified in 20.6% (139/675) of CRC cases. Interestingly, CARD10 amplification was found to be significantly associated with CARD10 protein expression assessed by immunohistochemistry (IHC) in our cohort of CRC cases (p=0.0330). CARD10 amplification was also significantly associated with survival protein; c-Met (p=0.0175) and anti-apoptotic marker; XIAP (p=0.005), although no significant association was detected with any clinical parameters. In addition, we also sequenced 150 CRC for CARD10 mutations and found that CARD10 mutations were absent in our cohort of CRC samples. We also re-stained our tissue microarray slides of CRC cases for CARD10 expression using a new antibody for cytoplasmic staining. Our results were comparable with nuclear staining and 19.4% (127/655) CRC cases were found to have over-expression of CARD10. We also analyzed over-expression of CARD10 with MSI status and other molecular markers such as BRAF mutations and found that there was no association between MSI status and BRAF mutations with CARD10 expression. However, we went ahead and analyzed our cohort of CRC for BRAF mutations. We found a very low incidence of BRAF mutations (2.5%) in our cohort of CRC samples. The most common BRAF mutation found in our cohort was V600E which constituted 90% of all mutations found.

In this study, we examined the co-expression of Cox2 and FoxM1 in our cohort of clinical samples and determined the efficiency of targeting both the proteins simultaneously using small molecular inhibitors for apaoptosis and regression of xenograft tumors.

The study is illustrated below:

BACKGROUND: Cross-talk between deregulated signaling pathways in cancer cells causes uncontrolled growth and proliferation. These cancers cells become more aggressive and quickly develop resistance to therapy. Therefore targeting of these deregulated pathways simultaneously can result in efficient cell death of cancer cells. In this study we investigated co-expression of Cox-2 and FoxM1 in a cohort of colorectal carcinoma (CRC) samples and also examined whether inhibition of Cox-2 and FoxM1 simultaneously can lead to inhibition of cell viability and induction of apoptosis in colorectal cancer cell lines and *in vivo* xenografts.

METHODS: Protein expression of Cox-2 and FoxM1 was determined in a large cohort of 770 clinical CRC samples in a tissue micro-array format by immunohistochemistry. Cell death was measured using live dead assay. Apoptosis was measured by annexin V/PI dual staining. Immunoblotting was performed to examine the expression of proteins. Calcusyn software was utilized to estimate the synergistic doses using chou and Talalay method.

RESULTS: Co-expression of Cox-2 and FoxM1 was detected in 33.3% (232/697) of CRC's and associated with an aggressive phenotype characterized by younger age (p=0.0191), high proliferative index marker; Ki-67 (p=0.004) and MMP-9 (p=0.0116) as well as activation of AKT (p=0.0214). *In vitro*, inhibition of FoxM1 and Cox-2 with pharmacological inhibitors; Thiostrepton and NS398 resulted in efficient down-regulation

of FoxM1 and Cox-2 expression along with inactivation of AKT and inhibition of colony formation, invasion and migratory capability of CRC cells. In addition, there was also inhibition of cell viability and induction of apoptosis via the mitochondrial apoptotic pathway in CRC cell lines. Finally, treatment of CRC xenograft tumors in nude mice with combination of Cox-2 and FoxM1 inhibitors inhibited tumor growth significantly via down-regulation of Cox-2 and FoxM1 expression.

CONCLUSIONS: These findings demonstrate that co-expression of Cox-2 and FoxM1 might play a critical role in the pathogenesis of CRC. Therefore, targeting of these pathways simultaneously with sub toxic doses of pharmacological inhibitors can be a potential therapeutic approach for the treatment of this subset of CRC.

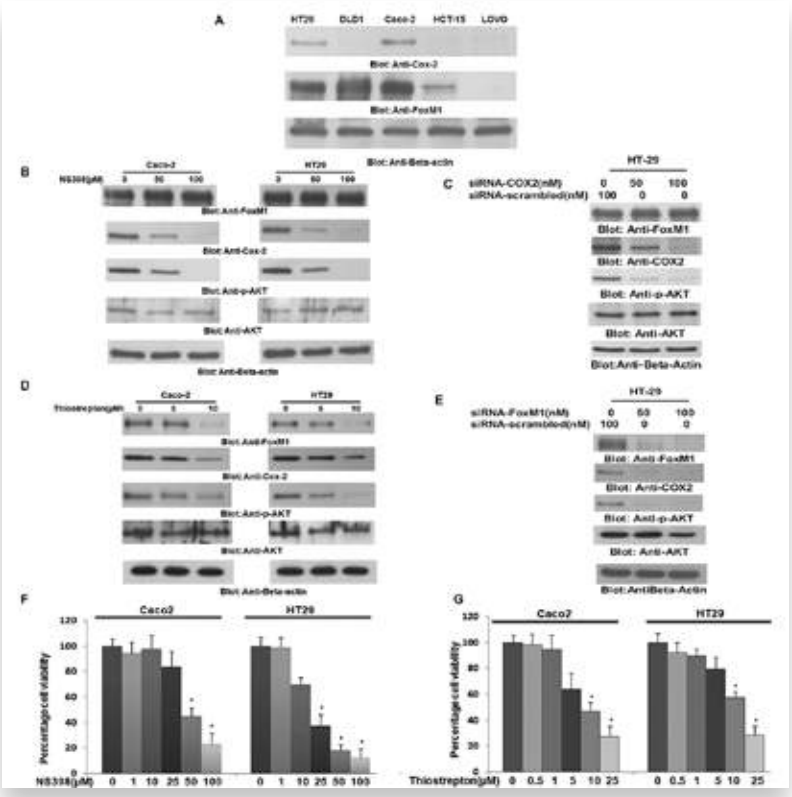


Figure 5. NS398 and Thiostrepton inhibits cell viability in CRC cell lines **(A)** HT29, DLD1, Caco-2, HCT-15 and LOVO cells were lysed and immuno-blotted with Cox-2, FoxM1 and Beta-actin antibodies **(B)** Caco-2 and HT29 cell lines were treated with 50 and 100μM NS398 for 48 hours. Proteins were lysed and immunoblotted with antibodies against FoxM1, Cox-2, p-AKT, total AKT and Beta-actin. **(C)** HT29 cells were either transfected with 50 and 100nM siRNA, specific against Cox-2 or scrambled siRNA for 48 hours. Cells were lysed and equal amounts of proteins were immuno-blotted with antibodies against FoxM1, Cox-2, p-AKT, total AKT and Beta-actin. **(D)** Caco-2 and HT29 cell lines were treated with 5 and 10μM Thiostrepton for 48 hours. Proteins were lysed and immunoblotted with antibodies against FoxM1, Cox-2, p-AKT, total AKT and Beta-actin. **(E)** HT29 cells were either transfected with 50 and 100nM siRNA, specific against FoxM1 or scrambled siRNA for 48 hours. Cells were lysed and equal amounts of proteins were immuno-blotted with antibodies against FoxM1, Cox-2, p-AKT, total AKT and beta-actin. **(F)** Caco-2 and HT29 cell lines were incubated with 0-100μM NS398 for 48 hours. Cell viability was measured by MTT assays as described in Materials and Methods. The graph displays the mean +/- SD (standard deviation) of three independent experiments, * $p < 0.05$, statistically significant (Students t-test). **(G)** Caco-2 and HT29 cell lines were incubated with 0-25μM Thiostrepton for 48 hours. Cell viability was measured by MTT assays as described in Materials and Methods. The graph displays the mean +/- SD (standard deviation) of three independent experiments, * $p < 0.05$, statistically significant (Students t-test).

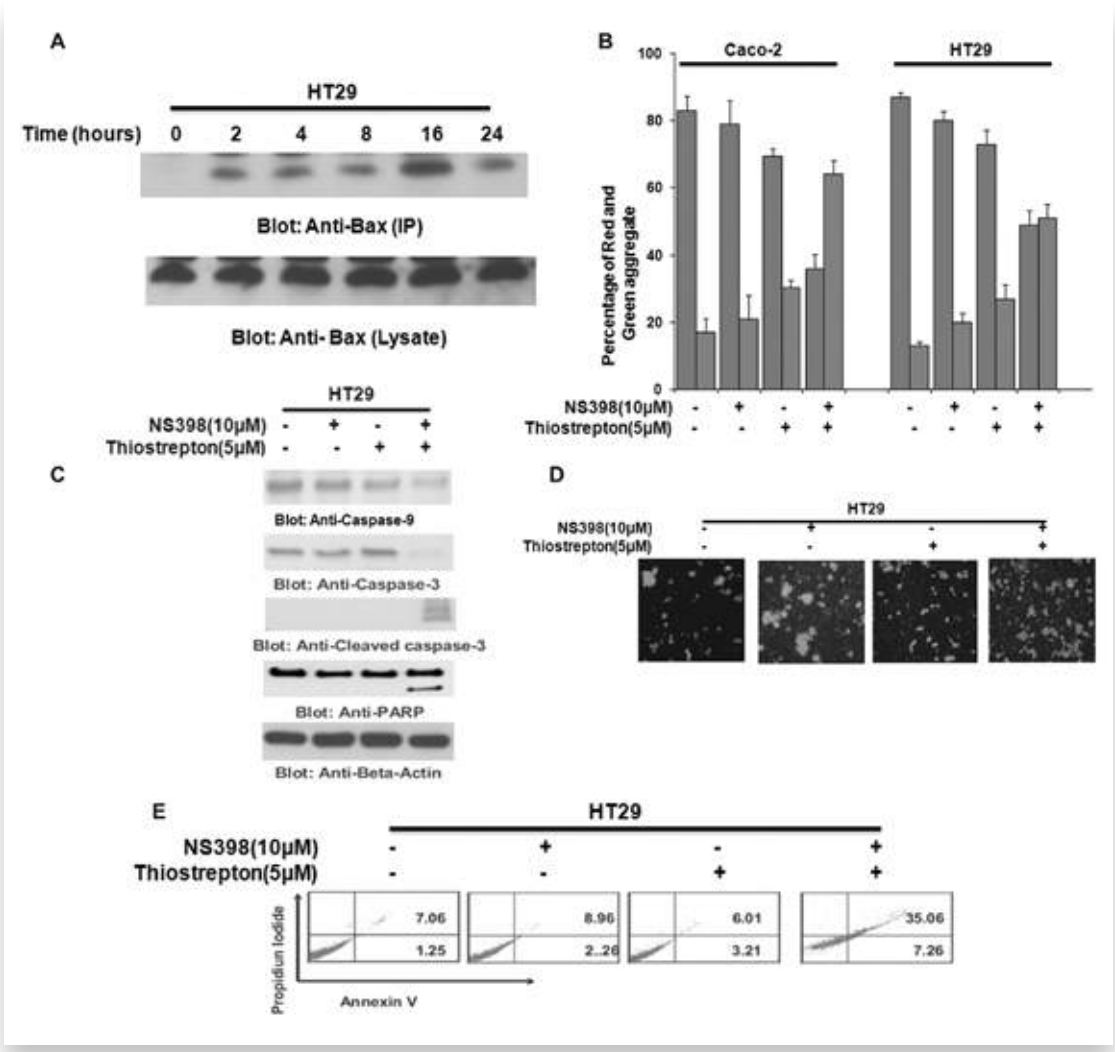


Figure 6. Combination of NS398 and Thiostrepton at sub-optimal doses induces caspase-dependent apoptosis via the mitochondrial pathway in CRC cells. (A) HT29 cells were treated with combination of 10μM NS398 and 5μM Thiostrepton for indicated time periods. Cells were lysed in 1% Chaps lysis buffer and subjected to immuno-precipitation with anti-Bax 6A7 monoclonal antibody and probed with specific polyclonal anti-Bax antibody for detection of conformationally changed Bax protein. In addition, the total cell lysates were applied directly to SDS–PAGE, transferred to immobilon membrane and immuno-blotted with specific anti-Bax polyclonal antibody. (B) Caco-2 and HT29 cells were treated with 10μM NS398 and 5μM Thiostrepton either alone or in combination for 48 hours. Live cells with intact mitochondrial membrane potential (red bars) and dead cells with lost mitochondrial membrane potential (green bars) was measured by JC-1 staining and analyzed by flow cytometry as described in Materials and Methods. The graph displays the mean +/- SD (standard deviation) of three independent experiments. (C) HT29 cells were treated with 10μM NS398 and 5μM Thiostrepton alone or in combination for 48 hours. Cells were lysed and equal amounts of proteins were immunoblotted with antibodies against caspase-9, caspase-3, cleaved caspase-3, PARP, and Beta-actin. (D) Caco2 and HT29 cells were treated with 10μM NS398 and 5μM Thiostrepton either alone or in combination for 48 hours and cell death was analyzed by Live/Dead Assay. (E) HT29 cells were treated with 10μM NS398 and 5μM Thiostrepton alone or in combination for 48 hours. Thereafter, the cells were washed, and stained with annexin V/propidium iodide, and analyzed by flow cytometry as described in Materials and methods

PROJECT TITLE: Identifying Molecular Signature of Thyroid Cancer Using Next Generation Technology Based on International Cancer Genome Consortium (ICGC) Guidelines

RAC# 2110 031

Thyroid cancer is currently the second most common cancer in females after breast cancer in Saudi Arabia. Incidence of thyroid cancer is also gradually increasing in Saudi Arabia. Thyroid cancer contributed 1.5% to 3.8% of all cancers diagnosed in the Middle East Cancer Consortium (MECC) countries annually, which was generally higher than the proportion in the United States (1.6%). The prognosis for PTC is often favorable, however, ~20% of PTC tumors recur and some reach advanced stages. However, the factors and mechanisms determining the aggressive behavior of some papillary carcinomas are not yet completely understood. Molecular alterations enabling targeted cancer therapy have not been identified for thyroid cancer. The whole genome sequencing of thyroid cancers from our study will generate comprehensive catalogues of somatic mutations in 500 papillary thyroid cancers under the ICGC model by high coverage, shotgun genome sequencing of both tumor and normal DNA. This comprehensive cataloguing of the genetic alterations will yield a full range of somatic mutations including single-nucleotide variants, insertions, deletions, copy number changes, translocations and other chromosomal rearrangements and provide new insights into the process of thyroid carcinogenesis for individual tumor as well as subtypes. As proposed in this project our investigation will identify high quality catalogue markers for the prediction of clinical behavior of aggressive thyroid tumors. Thyroid Cancer samples are being collected after the surgery is performed at King Faisal Specialist Hospital and processed in the Department of Pathology. If the tumor area is equal to or more than 80% of the specimen, a scraping of the sample is given for DNA extraction. All images are stored in Aperio Scansope and in the ArcturusXT™ LCM instrument. Genomic DNA was extracted by using QIAGEN DNA extraction kit. Library preparation was performed using standard Illumina protocols. Data generated by Illumina Hiseq 2500 is initially processed by the Consensus Assessment of Sequence and Variation (CASAVA) software. The mapped reads are stored in bam format and the bam files are used for SNP calling and structural variation analysis. To date, out of 543 clinical samples collected, 101 paired samples of PTC and normal tissue/blood have been sequenced. These include 9 Whole Genome Sequencing and 92 whole exome sequencing.

RESULTS OF 101 EXOME SEQUENCING:

PTC in our cohort of 101 cases showed on average 0.82 nonsynonymous somatic mutations per Mb. Surprisingly, one of the 101 samples accounted for nearly 83% of all somatic mutations (16,821, compared to a total of 20,118 from all remaining samples). When excluded, the average dropped to 0.23 nonsynonymous somatic mutation per Mb, which is comparable to what was reported by the Cancer Genome Atlas Research Network data (0.41), and comparatively lower than other cancers (bladder=7.1, breast=1.2, colorectal=3.1, head and neck=3.9, ovarian=1.7) (Figure 7A). The minimum density in our cohort is 0.00/MB and the maximum is 1.21/MB with median at 0.21/MB).

We performed duo analysis of WES from PTC and corresponding normal tissue to search for genes with at least two somatic mutations in our cohort of 101 samples. In addition to the MAPK signaling pathway genes mentioned above (BRAF, NRAS and HRAS), we identified 21 genes (Table 1) that are recurrently mutated in PTC tissues. We show that the novel genes with the highest frequency of

somatic mutations are DNMT3A (3.96%), PKHD1 (2.97%), SPTBN5 (0.99%), TP53 (1.98%), DNAH1 (1.98%), CABIN1 (1.98%) and MACC1 (0.99%) (Table 1)(Figure 7).

Table 1. Recurrent Somatic Mutations from Exome & Capture Cohort.

S.No.	Gene Name	Exome 101 Cohort			
		# Mutations	# Samples	Total	Freq
1	BRAF	60	60	101	59.41
2	NRAS	1	1	101	0.99
3	TG	2	2	101	1.98
4	HRAS	2	2	101	1.98
5	DNMT3A	4	4	101	3.96
6	PKHD1	3	3	101	2.97
7	SPTBN5	2	1	101	0.99
8	TP53	2	2	101	1.98
9	DNAH1	2	2	101	1.98
10	CABIN1	2	2	101	1.98
11	MACC1	2	1	101	0.99
12	GPR98*	2	2	101	1.98
13	SNED1	2	2	101	1.98
14	TRIOBP	2	1	101	0.99
15	LTBP2	3	1	101	0.99
16	CAMKK2	2	2	101	1.98
17	ATP8B2	2	1	101	0.99
18	MLXIPL	2	2	101	1.98
19	GLRA3	2	1	101	0.99
20	NEFH	2	2	101	1.98
21	ZNF677	2	1	101	0.99
22	DENND4B	2	1	101	0.99
23	CRTAM**	2	1	101	0.99
24	SMU1	2	1	101	0.99

* Not validated by sanger **Two hits in same codon in exome data

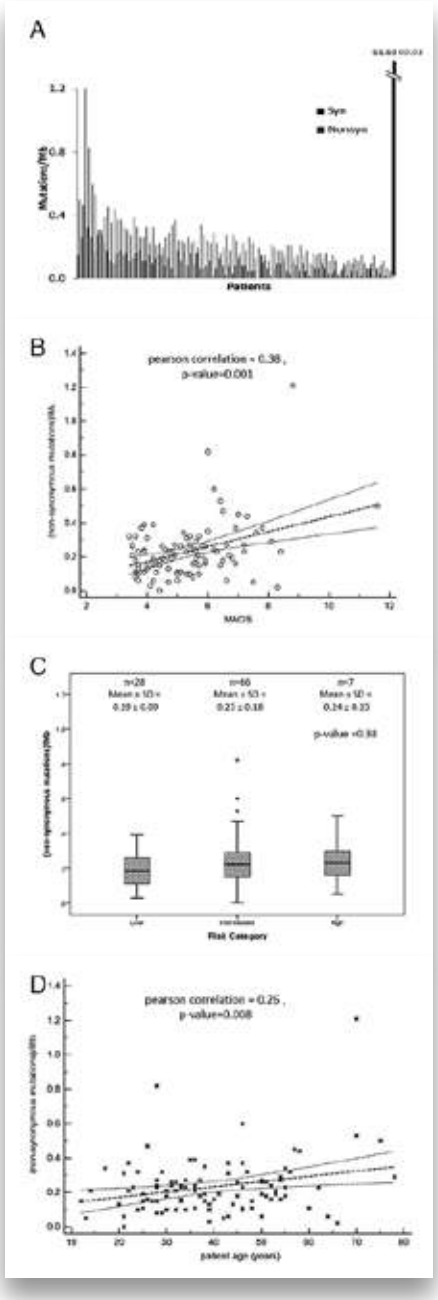


Figure 7. (A) Mutation density (in MB) in 101 PTC exome cohort. The maximum mutation density is 1.2 MB. Synonymous mutation density is compared with non-synonymous.(B) Correlation of non-synonymous mutation density with MACIS score for mortality risk which is significant (p=0.001). (C) Correlation of non-synonymous mutation density with risk of recurrence (p=0.38). (D) Correlation of non-synonymous mutations with patient's age (p=0.008). (One outlier case was excluded for figure presentation in B, C and D).

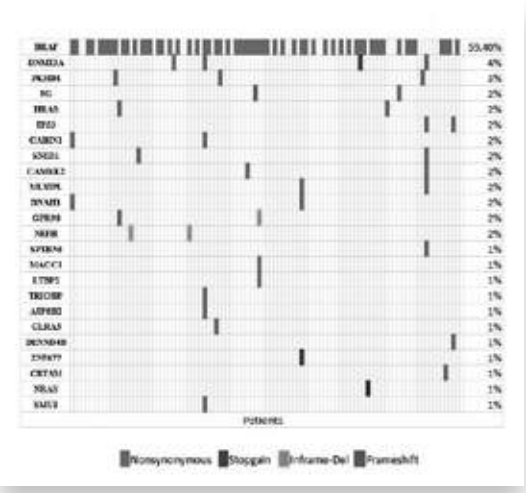


Figure 8. Frequency and types of mutation in 24 genes detected by exome sequencing. Majority of mutations are missense with two stop-gains, three in-frame deletions and one frame-shift mutation.

PROJECT TITLE: Prognostic Significance of Molecular and Genetic Alterations in Saudi Arabian Breast Cancers
RAC# 2140 008

Ethnic differences of breast cancer genomics have prompted us to investigate the spectra of BRCA1 and BRCA2 mutations in different populations. The prevalence and effect of BRCA 1 and BRCA 2 mutations in Middle Eastern population is not fully explored. We conducted this study to characterize the prevalence of BRCA mutations in Middle Eastern breast cancer patients. A total of 410 clinically high risk breast cancer patients were enrolled in the two-tiered study. BRCA mutation screening was performed using Capture sequencing and/or Sanger sequencing. 19 STR markers were used for founder mutation analysis. Among 163 cases enrolled in screening set, 9 different types of deleterious mutation were identified in 12 (12/163, 7.4%) cases, 10 (10/12, 83.3%) in BRCA 1 and two (2/12, 16.7%) in BRCA 2. In the validation set of 247 cases using a panel of the 9 mutations identified in screening set, six types of mutation were identified in 14 (5.7%, 14/247) cases, 13 in BRCA 1, and one in BRCA 2. Taken all together, this validation screening panel could identify 77.0% (5.7% vs. 7.4%) of all mutant cases. Six recurrent mutations accounted for 88.5% (23/26) of all the mutant cases. Haplotype analysis was performed to confirm c.1140 dupG and c.4136_4137delCT mutations as novel putative founder mutation, accounting for 46.2% (5+7/26) of all BRCA mutant cases and 2.9% (5+7/410) of all the breast cancer cases respectively. BRCA-1 mutation was significantly associated with BRCA-1 protein expression loss (p=0.0003). In this study, our findings suggest that BRCA mutations account for a substantial proportion of clinically high risk breast cancer in Middle Eastern population. Identification of the spectrum of mutation, founder effect and prevalence in Middle Eastern population facilitates genetic counseling, risk assessment and development of cost-effective screening strategy.

PROJECT TITLE: Anti-Tumor Activity of XIAP Inhibitor Embelin on Mice Xenografts of Epithelial Carcinomas
RAC# 2110 025

X-linked inhibitor of apoptosis protein (XIAP) also known as inhibitor of apoptosis protein 3 (IAP3) and baculoviral IAP repeat-containing protein 4 (BIRC) that in humans is encoded by the XIAP gene. Through their ability to inhibit caspases, IAPs act as anti-apoptotic proteins and therefore are promising therapeutic targets. XIAP inhibits caspase 3, 7, and 9 but not caspases 1, 6, 8 or 10. Inhibition of XIAP by antisense strategies or peptides that bind and inhibit the BIR3 domain of XIAP sensitizes malignant cells to chemotherapy. XIAP expression is found to be correlated with a poor clinical outcome in various cancers. XIAP has been found to be associated with various survival pathways including PI3-kinase/AKT pathway and there is a strong evidence for a function relationship between AKT and XIAP in cancer cells, XIAP expression is regulated by PI3K

and AKT activity in cancer cells. In addition, XIAP has also been found to be associated with other survival pathways including NFκB, c-Met and FASN. We therefore hypothesize that targeting XIAP by specific inhibitors will inhibit tumor growth via induction of apoptosis in tumor cell xenografts *in vivo*.

PROJECT TITLE: Prognostic Significance of Genetic Alterations in Saudi Colorectal Cancers
RAC 2080 030

In this year, we categorized the CRC cases into 3 major molecular pathways; namely Traditional, Alternate and Serrated. Cases which could not be assigned were kept under Unassigned group. We then calculated the incidence of each pathway in our population and correlated them with clinicopathological parameters.

Colorectal cancer (CRC) is one of the common cancers in the world. In Saudi Arabia, CRC is the most common cancer in males and third most common in females. A newly proposed integrated pathways comprising traditional, alternate and serrated by genetic and epigenetic factors was defined recently and hypothesized to role in the pathogenesis of CRC; however there is a paucity of information about these proposed molecular pathways in different ethnic group. Hence we analyzed a large cohort of Saudi colorectal tumors to understand the role of these molecular pathways. 770 archival CRCs specimen were evaluated for Microsatellite Instability (MSI), BRAF, KRAS and 500 cases for CpG Island Methylator Phenotype (CIMP). Traditional pathway constituted 33.4% of CRC cases; the alternate pathway comprised 11.6% of cases. Strikingly, the serrated molecular pathway accounted for only 0.8 % of Middle Eastern CRC that is extremely below to publish data. 54.2% CRC cases did not qualify to fit into any pathway and thus were designated an unassigned group. Molecular pathways were significantly associated with tumor site and grade. In our attempt to further classify unassigned group a subset of the uncategorized pathway showed a significant survival difference (p=0.0079). The Unassigned group that accounted for the majority of our cases reflects the heterogeneity of colorectal cancers and warrants the need to unravel the molecular genetic basis of this disease to further subcategorize these CRC cases. It also identifies the need to do further studies on different populations for better understanding of their exact role and incidence.

PROJECT TITLE: Molecular Signatures of Diffuse Large B-cell Lymphoma (DLBCL), Lung and Ovarian Cancer: A Pilot Study
RAC 2060 008

The clinical course of individual cancers is driven by the sum of molecular alterations in cancer cells. Accordingly, studies analyzing the expression of thousands of genes in tumors using cDNA and tissue microarrays have suggested a clinical relevance of the molecular signatures of cancers. However, limited information is available for many cancer types. Moreover, as increasing data suggest there are significant molecular differences between the same tumor types from patients of different ethnic backgrounds. It is unclear to what extent conclusions from foreign studies will apply to Saudi cancer patients. The proposed pilot project is intended to look for molecular signatures (or individual gene alterations) in diffuse large B-cell lymphoma (DLBCL), lung neoplasm and ovarian cancer based upon DNA alterations including LOH, gene amplification and expression analysis based upon tissue and cDNA microarrays. This study will provide the basis for future projects aimed at investigating the correlation of molecular profiles of tumor subtypes with clinical parameters such as response to treatment and survival. In addition

larger studies based upon data from this project will establish ethnic diversity in the molecular profiles of different tumor subtypes. The discovery of significant molecular differences between Saudi and Caucasians cancers would challenge the current practice of treating Saudi cancer patients according to Western protocols.

PROJECT TITLE: Molecular Signatures of Cancer: Clinical Significance in Saudi Arabian and European Cancer Patients
RAC 2040 004

The proposed project is intended to look for clinically relevant molecular signatures (or individual gene alterations) in breast, kidney, liver, and colon cancers using a combined DNA- CGH and tissue microarray approach in Saudi and European cancers. The combination of I) a large scale initial expression screening using DNA microarrays, II) the possibility to systematically compare expression data with DNA copy number changes, and III) the opportunity of validating individual alterations on a large set of tissue microarrays is unique. These studies will most likely lead to the identification of clinically relevant genes or gene sets and at the same time provides extensive information on possible genetic differences between Saudi and European cancers. The discovery of significant molecular differences between Saudi and Caucasians cancers would challenge the current praxis of treating Saudi cancer patients according to Western protocols.

BREAST CANCER

Anaplastic lymphoma kinase (ALK) gene has been found to be altered in several solid and hematological tumors. We aimed to comprehensively study the prevalence ALK expression, changes in copy number and translocation in a large cohort of Breast cancer cases in Middle Eastern population. ALK protein expression was investigated by immunohistochemistry and numerical & structural variation of ALK gene was analyzed by Fluorescent In-Situ Hybridization (FISH) in a tissue microarray format in a cohort of more 1000 Middle Eastern Breast cancers. The data were correlated with clinicopathological parameters and other important molecular biomarkers. Immunohistochemical analysis showed ALK overexpression in 36.0% of the Breast cancer patients and gene amplification was present in 13.3% of cases, seen by FISH analyses. ALK overexpression was significantly associated with ALK gene amplification (p=0.0031). ALK over-expressing tumors showed significant association with high grade tumors (p=0.0039), ductal histological subtype (p=0.0076), triple negative phenotype (p=0.0034), high Ki-67 (p<0.0001) and p-AKT (p<0.0001). Immunohistochemical analysis showed ALK is overexpressed in substantial proportion of breast cancers and possibly plays a significant role in the aggressive behavior of this cancer. Gene amplification is hypothesized to be a possible cause for a significant proportion of this overexpression. Based on these findings, a potential role of ALK inhibitor as a therapeutic agent, targeting aggressive subtype of breast cancer merits further investigation.

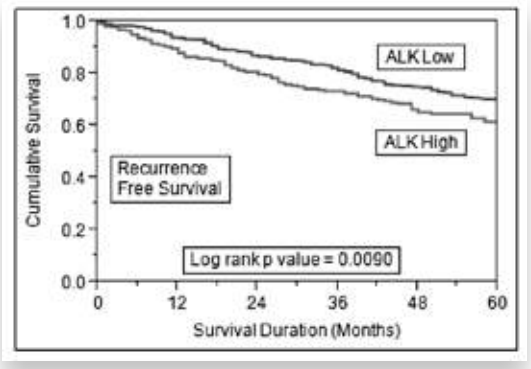


Figure 9. Kaplan-Meier survival analysis for the prognostic significance of ALK expression in breast cancer. Breast cancer patients with overexpression of ALK had reduced 5 year Recurrence Free Survival compared with those showing low expression of ALK (p=0.0090).

The significance of the role of PTEN in Middle Eastern ethnic breast cancer has not been explored especially with the fact that breast cancer originating from this ethnic population tend to behave more aggressively than breast cancer in the west. In this study we analyzed PTEN alteration in a tissue microarray format containing more than 1000 primary breast cancers with clinical follow up data. Tissue Microarray sections were analyzed for protein expression and copy number change using immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH). Loss of PTEN immunostaining was observed in 77% of the cases. PTEN loss was significantly associated with large tumor size (p=0.0030), high grade (p=0.0281), tumor recurrence (p=0.0333) and Triple negative breast cancers (p=0.0086). PTEN loss in Triple negative breast cancers was significantly associated with rapid tumor cell proliferation (p=0.0396) and poor prognosis (p=0.0408). PTEN deletion was found only in 60 cases (6.4%) of cases. Loss of PTEN protein expression occurs at high frequency in Middle Eastern breast cancer. PTEN inactivation may potentially lead to an aggressive behavior of tumor cells through stimulation of tumor cell proliferation. Furthermore PTEN signaling pathway might be used as potential therapeutic target in Triple negative breast cancers since loss of its expression is shown to be significantly associated with this aggressive subtype of breast cancer.

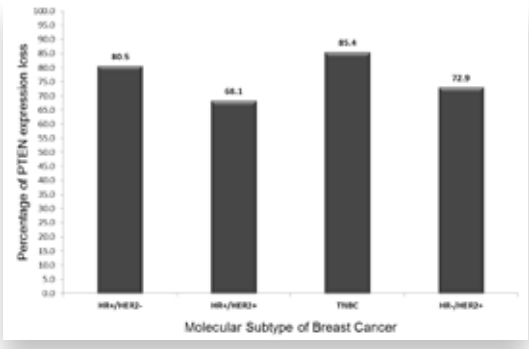


Figure 10. Bar diagram showing proportion of PTEN expression loss by IHC in different molecular subtypes of Middle Eastern breast cancer.

COLORECTAL CANCER

In the current year a comprehensive molecular characterization was performed in a cohort of 807 CRC by immunohistochemical and microsatellite analysis by PCR; BRAF mutation screening, CIMP high phenotype; and analysis for germline mutations in 425 CRC samples. These were all MSI-H samples (n=91), all MSI-L samples (n=143) and selected cases from the MSS groups (n=191) that met Revised Bethesda guidelines. PCR identified 91 MSI-H (11.3%) cases and Sequencing revealed MMR germline mutations in 8 CRC cases only. These 8 cases (0.99%) of 807 CRC were MSI-H, met the Revised Bethesda guidelines and did not harbor BRAF mutations. Our study confirmed LS cases in ≈1.0% CRC and reflects the efficacy of screening of MSI-H cases that lack BRAF mutations. This comprehensive study from Saudi Arabia will help in implementing the universal screening/reflex testing strategy in a clinical setting in Saudi Arabia and conducting a national screening program benefitting patients and their relatives.

We also carried out the molecular characterization of 770 CRCs specimen for Microsatellite Instability, BRAF & KRAS by PCR and 500 cases for CpG Island Methylator Phenotype (CIMP) High phenotype by Methyl light technology. Tumors were assigned to different molecular pathways and studied for clinicopathological correlation and survival analysis. Traditional pathway constituted 33.4% of CRC cases; the alternate pathway comprised 11.6% and serrated molecular pathway accounted for only 0.8 % of Middle Eastern CRC. 54.2% CRC cases did not qualify to fit into any pathway and thus were designated an unassigned group. Molecular

pathways were significantly associated with tumor site and grade. A subset of uncategorized pathway showed a significant survival difference (p=0.0079). Serrated pathway accounts for a very low proportion of our CRC patient cohort. The Unassigned group accounted for the majority of Middle Eastern CRC cases, so current method of CRC pathway analysis might not be applicable to this ethnic group. This study warrants the need to unravel the molecular genetic basis of this disease to further subcategorize these CRC cases. It also identifies the need to do further studies on different populations for better understanding of their exact role and incidence.

RESEARCH PROJECTS

ACTIVE PROJECTS

1. RAC 2140 033 (NSTIP 10-BIO963-20-R). The Role of FoxM1 in Saudi Arabian Epithelial Ovarian Cancer. Grant funded project by National Science, Technology and Innovation Plan (NSTIP).
2. RAC 2140 010 (NSTIP 11-BIO2219-20). Role of XIAP in Pathogenesis of Saudi Arabian Papillary Thyroid Carcinoma. Principal Investigator. Grant funded project by National Science, Technology and Innovation Plan (NSTIP).
3. RAC 2140 005 (NSTIP 10-BIO959-20). Prognostic Significance of CARD10 in Saudi Colorectal Cancers. Grant funded project by National Science, Technology and Innovation Plan (NSTIP).
4. RAC 2140 008. Prognostic Significance of Molecular and Genetic Alterations in Saudi Arabian Breast Cancers.
5. RAC 2120 021. Identification of C-Met Expression and Its Association with Other Survival Markers for Diagnostic Purposes and Risk Stratification in Saudi Arabian Lung Cancer.
6. RAC 2110 031. Identifying of Molecular Signature of Thyroid Cancer Using Next Generation Technology Based on International Cancer Genome Consortium (ICGC) guidelines.
7. RAC 2110 025. Anti-tumor Activity of XIAP Inhibitor Embelin on Mice Xenografts of Epithelial Carcinomas.
8. RAC 2080 030. Prognostic Significance of Genetic Alterations in Saudi Colorectal Cancers.
9. RAC 2060 008. Molecular Signatures of Diffuse Large B-cell Lymphoma (DLBCL), Lung and Ovarian Cancer: a pilot study.
10. RAC 2040 004. Molecular signatures of cancer: Clinical Significance in Saudi Arabian and European Cancer Patients.

COMPLETED PROJECTS

1. RAC 2080 029. Clyclooxygenase: Target for Epithelial Ovarian Cancer Prevention and Treatment.
2. RAC 2080 031. Role of c-MET in Saudi Arabian Papillary Thyroid Carcinoma for Novel Therapy.
3. RAC 2120 017. Prevalence of Constitutional Mismatch Repair Deficiency (CMMRD) Syndrome in Saudi Pediatric Acute Lymphoblastic Leukemia. Grant funded project by SANAD.
4. RAC 2070 004. Role of PI3-kinase-AKT Pathway in Epithelial Carcinomas.
5. RAC 2050 015. Translation Initiatives in Lymphoid Malignancies.
6. RAC 2041 046. Retrospective Review of Pediatric Patients Diagnosed with Hodgkin Lymphoma Treated at KFSH&RC.
7. RAC 2030 019. Clinicopathologic Study of Diffuse Large B-cell Lymphoma and Outcome Prediction at KFSH&RC.

8. RAC 2030 040. Gene Amplification and Over Expression Survey in Multi Tumor Tissue Array from Saudi Arabia.

PUBLICATIONS

ACCEPTED/PUBLISHED ARTICLES

- Shi X, Liu R, Basolo F, Giannini R, Shen X, Teng D, Guan H, Shan Z, Teng W, Musholt TJ, Al-Kuraya K, Fugazzola L, Colombo C, Kebebew E, Jarzab B, Czarniecka A, Bendlova B, Sykorova V, Sobrinho-Simões M, Soares P, Kee Shong Y, Yong Kim T, Cheng S, Asa SL, Viola D, Elisei R, Yip L, Mian C, Vianello F, Wang Y, Zhao S, Oler G, Cerutti JM, Puxeddu E, Qu S, Wei Q, Xu H, O'Neill CJ, Sywak MS, Clifton-Bligh R, Lam AK, Riesco-Eizaguirre G, Santisteban P, Yu H, Tallini G, Holt EH, Vasko V, Xing M. Differential Clinicopathological Risk and Prognosis of Major Papillary Thyroid Cancer Variants. *J Clin Endocrinol Metab*. 2015 Nov 3.
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- Siraj AK, Prabhakaran S, Bavi P, Bu R, Beg S, Al Hazmi M, Al-Rasheed M, Al-Assiri M, Sairafi R, Al-Dayel F, Al-Sanea N, Uddin S, Al-Kuraya K. Prevalence of Lynch Syndrome in a Middle Eastern Population with Colorectal Cancer. *Cancer*. 2015 Jun 1;121(11):1762-71.

ABSTRACTS

- Al-Kuraya K, Al-Dayel F. Triple Negativity in Saudi Arabian Breast Cancer. IMPAKT Breast Cancer Conference 2015, May 7-9, 2015, Brussels, Belgium.
- Bu R, Prabhakaran S, Beg S, Jehan Z, Siraj AK, Ahmed M, Hussain A, Al Sobhi S, Al-Dayel F, Uddin S, Al-Kuraya K. ALK overexpression is associated with activation of PI3K/AKT signaling pathway in

PTC. AACR Annual Meeting 2015, April 18-22, 2015, Philadelphia, Pennsylvania, USA.

- Ahmed M, Hussain A, Begum R, Thangavel S, Ajarim D, Beg S, Uddin S, Al-Kuraya K. Over-expression of FoxM1 in breast cancer can be therapeutically targeted using thiostrepton. AACR Annual Meeting 2015, April 18-22, 2015, Philadelphia, Pennsylvania, USA.
- Siraj AK, Beg S, Prabhakaran S, Jehan Z, Ajarim D, Ahmed M, Al-Dayel F, Tulbah A, Al-Kuraya K. PTEN loss is associated with aggressive behavior and poor prognosis in Middle Eastern triple negative breast cancer. AACR Annual Meeting 2015, April 18-22, 2015, Philadelphia, Pennsylvania, USA.
- Hussain A, Ahmed M, Bu R, Beg S, Alrashed A, Melosantos R, Ajarim D, Uddin S, Al-Kuraya K. XIAP over-expression is a poor prognostic marker in breast cancer and can be targeted to induce efficient apoptosis. AACR Annual Meeting 2015, April 18-22, 2015, Philadelphia, Pennsylvania, USA.
- Beg S, Prabhakaran S, Bu R, Al-Assiri M, Sairafi R, Al-Dayel F, Al-Sanea N, Siraj AK, Uddin S, Al-Kuraya K. Molecular markers and pathways analysis of Middle Eastern Colorectal Carcinoma. AACR Annual Meeting 2015, April 18-22, 2015, Philadelphia, Pennsylvania, USA.

DEPARTMENT OF INFECTION AND IMMUNITY

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THE DEPARTMENT OF INFECTION AND IMMUNITY (DII) WAS established in early 2011. It now contains four research Sections, namely Immunocompromised Host (IH), Microbial Pathogenesis (MP), Molecular Virology (MV), and Mycobacteriology (MB). DII concentrates on studying the molecular mechanisms through which microbes cause disease in infected individuals and on understanding the relationship between microbes and their hosts. These studies should enable more preventive methods and trigger further research and development in drug and vaccine manufacturing advances. State-of-the-art techniques are used to achieve this goal. DII also fosters collaboration with other Departments within our institution and with other institutions with interests in investigations related to microbes or microbial diseases. Specific microbes that are dealt with include human hepatitis viruses, human papillomaviruses, human immunodeficiency viruses, human respiratory viruses, antimicrobial resistance, *Mycobacterium tuberculosis* and other mycobacteria, *Brucella melitensis*, malaria parasites, and microbes infecting renal transplant patients. Services to the institution and others include determination of bacterial strains and tracing the source of bacterial infection using pulsed-field gel electrophoresis and multilocus sequence typing technologies. The Department constantly designs and develops technologies for the identification and detection of emerging and re-emerging pathogens, provides services for DNA fingerprinting of nosocomial bacteria, trains Saudi nationals in advanced microbiological methods, and collaborates with scholars from national, regional and international destinations.

LIST OF RAC APPROVED PROJECTS

PROJECT TITLE: Correlation Between Genetic Variations and Serum Level of Interleukin 28B with Virus Genotypes and Disease Progression in Chronic Hepatitis C Virus Infection

RAC Approval #: 2090001

Source of Funding: KACST

DESCRIPTION: Recent studies have demonstrated polymorphisms near the interleukin 28B (IL-28B) gene could predict the response to Peg-IFN-a/RBV combination therapy in HCV-infected patients. The aim of the study was to correlate the serum level of IL28B in HCV-infected patients with virus genotype/subgenotype and disease progression. IL28B Serum level was detected and variations at five single nucleotide polymorphisms (SNPs) in IL28B gene region were genotyped and analyzed. The variation of IL28B genetic polymorphisms were found to be strongly associated with HCV infection when healthy control group was compared to HCV-infected patients with all p values <0.0001. Functional analysis revealed that subjects carrying rs8099917-GG genotype had higher serum level of IL28B than those with GT or TT genotypes (p = 0.04) (Table 1). Also, patients who were presented with cirrhosis (Cirr) only or with cirrhosis plus hepatocellular carcinoma (Cirr+HCC) had higher levels of serum IL28B when compared to chronic HCV-infected patients (p = 0.005 and 0.003, respectively) (Table 2). No significant association was found when serum levels of IL28B were compared to virus genotypes/sub-genotypes. This study indicates that variation at SNP rs8099917 could predict the serum levels of IL28B in HCV-infected patients. Furthermore, IL28B serum level may serve as a useful marker for the development of HCV-associated sequelae.

Table 1. Correlation of average IL28B concentration levels with the genotypes of rs8099917.

	Value	Std. Error	t-value	p-value
(Intercept)	1.586	0.025	58.82	0
rs8099917-GT	0.057	0.049	1.16	0.25
rs8099917-GG	0.115	0.057	2.03	**0.04**

Note: results for "intercept" correspond to "GG" genotype; i.e. log10 (conc.) = 1.586 for TT genotype, with ~0.06 increase in log10 (conc.) with each additional G-allele.

Table 2. Correlation of Average IL28B concentration levels with different outcome of HCV infection.

	Value	Std. Error	t-value	p-value
(Intercept)	1.461	0.027	54.77	0
Group 2	0.161	0.057	2.82	**0.005**
Group 3	0.126	0.161	0.79	0.43
Group 2+3	0.156	0.053	2.95	**0.003**

Note:results for "intercept" correspond to group = 1; i.e. log10 (conc.) = 1.46 for group 1 samples, with ~0.16 increase in log10 (conc.) for group 2 samples, and no additional sig. affect in log10 (conc.) for group 3 samples.

PROJECT TITLE: Characterization of H5N1 Influenza A Virus that Caused the First Highly Pathogenic Avian Influenza Outbreak in Saudi Arabia

RAC Approval #: 2100009

Source of Funding: KFSH&RC

DESCRIPTION: Saudi Arabia (SA) experienced a highly pathogenic avian influenza (HPAI) H5N1 outbreak in domesticated birds in 2007. Forty-three hemagglutinin (HA) and 41 neuraminidase (NA) genes of HPAI H5N1 viruses were sequenced and phylogenetic analyses of completely sequenced genes were performed to compare with other viral HA and NA gene sequences available in the public databases (Fig. 1). Molecular characterization of the H5N1 viruses revealed two genetically distinct clades, 2.2.2 and 2.3.1, of H5N1 viruses circulating in the area. Amino acid sequence analysis of the HA gene indicated that the virus from 2.2.2 contained the sequence SPQGERRRK-R/G at the cleavage site, while the virus from 2.3.1 contained the sequence SPQRERRRK-R/G. Additionally, a few mutations with amino acid substitutions such as M226I at N-link glycosylation site were identified in two of these isolates. Amino acid sequence of the NA gene showed a 20-amino-acid deletion in the NA stalk region, required for enhanced virulence of influenza viruses and its adaptation from wild birds to domestic chickens. As close contact between humans and birds is unavoidable, there is a need for a thorough understanding of the virus epidemiology, factors affecting the spread of the virus, and molecular characterization such as phylogeny and substitution rates of H5N1 viruses circulating in the region. Therefore, two genetically distinct clades were found to be circulating in the country, which could likely result in recombination and emergence of more virulent viral strains. These findings could be helpful for the authorities devising control measures against these viruses.

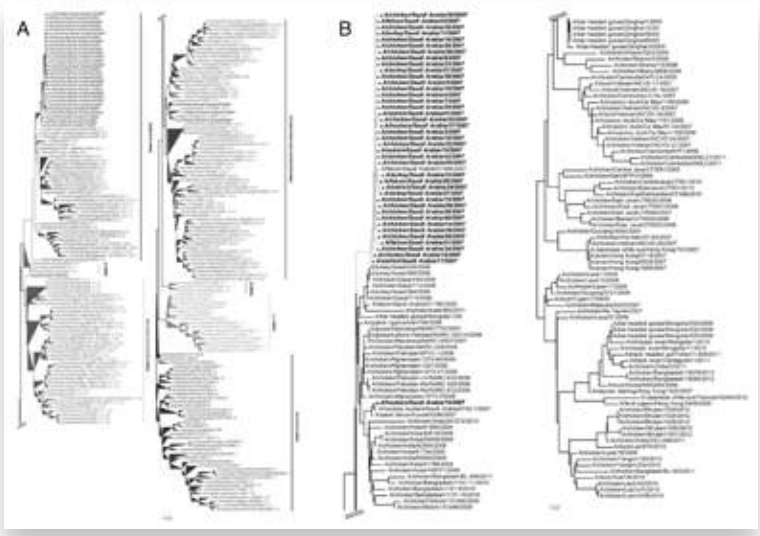

Figure 1. Phylogenetic analysis of HA sequences (A) and NA sequences (B). Neighbor-joining dendrogram based upon a Clustal W alignment of the HA and NA sequences determined here with selected HA and NA sequences available in the databases using MEGA 6.6 software. The database accession numbers of each sequence is given. The HA and NA genes from Saudi isolates are highlighted with colored rectangle. The numbers at nodes represent percentage bootstrap values (1,000 replicates).

PROJECT TITLE: Phylogenetic and Mutational Analysis of Influenza A (H1N1) Virus Isolates from Saudi Arabia
RAC Approval #: 2100009
Source of Funding: KFSH&RC

DESCRIPTION: In early 2009, a novel recombinant influenza A (H1N1) virus, containing gene segments from human, avian and swine influenza viruses, appeared in Mexico and rapidly disseminated worldwide. Little is known about the phylogeny and evolutionary dynamics of H1N1 found in Saudi Arabia. Understanding of the virus diversity and epidemiology is essential for devising resistance strategies. We aimed to establish the genetic relatedness of viral isolates from Saudi Arabia to the isolates around the world and to study the phylogenetics, mutation rate and substitution rate. We obtained 72 hemagglutinin (HA) and 45 neuraminidase (NA) sequences of the H1N1 virus from various regions of Saudi Arabia were characterized. Genetic characterization indicated that viruses from two different clades i.e., clade 6

Table 3. Comparison of gene sequences of Saudi Arabia H1N1 viruses with regional and global H1N1 isolates at key amino acid position in HA and NA genes.

Gene Position Isolates #	HA					NA*		
	83	203	222	293	321	106	248	275
HA/California/07/09	P	S	D	Q	I	V	N	Y
HA/Saudi Arabia/89/2009	S	T	D	Q	I	I	D	H
HA/Saudi Arabia/142/2009	S	T	D	Q	I	I	D	H
HA/Saudi Arabia/57/2009	S	T	D	Q	I	I	D	Y
HA/Hong Kong/ 2885/09	S	T	D	Q	V	I	D	H
HA/Bahrain/N11661/09	S	T	D	Q	V	I	D	H
HA/Amman/WRAIR1339N/09	S	T	D	Q	I	I	D	H
HA/Karaj/5924/10	S	T	D	Q	V	I	D	H
HA/Kuwait/N13093/09	S	S	D	Q	V	I	D	H
HA/Iraq/WRAIR1683P/09	P	S	D	Q	I	I	N	Y
HA/Sulaimani/05/09	S	T	D	Q	V	I	D	H
HA/Egypt/N14648/09	S	T	N	Q	I	I	D	H
HA/Ghom/169/10	S	T	D	Q	V	I	D	H

* Amino acids shown in this table for NA protein are of Saudi isolates NA/Saudi Arabia/22/2009, NA/Saudi Arabia/31/2009, NA/Saudi Arabia/08/2009.

Table 4. Mean substitution rates HA and NA proteins.

			Mutation rate	Mutation rate	Mutation rate	Mean rate (substitution/ nucleotide/year)
Model used	Gene	Number of sequences used	Codon position 1	Codon position 2	Codon position 3	
Relaxed clock +BSP	HA	49	0.725	0.928	1.34	$5.14x10^{-3}$
Relaxed clock +BSP	NA	39	0.493	1.036	1.473	$4.18x10^{-3}$

and 7 are circulating in the region, predominantly clade 7, the globally most widely circulating H1N1 clade. In this report, 72 hemagglutinin (HA) and 45 neuraminidase (NA) sequences of the H1N1 virus from various regions of Saudi Arabia were characterized. Sequence analysis of HA and NA genes showed high degree of sequence identity with corresponding genes of regional viruses circulating in South East Asia and type strain A/California/7/2009 (Table 3). New mutations were identified in HA gene of pH1N1 viruses that could alter the viral fitness. E374K in the HA was increasingly noted in 2 Saudi isolates and its co-occurrence with V30A was also observed in recent isolates. Relaxed clock and Bayesian Skyline Plot analysis based on all Saudi isolates and closely related global representatives indicated a little higher substitution rates (5.14×10^{-3} and 4.18×10^{-3} substitutions/nucleotide/year) when compared earlier reports (3.92×10^{-3} and 3.61×10^{-3} substitutions/nucleotide/year) (Table 4). Antigenic site of HA gene of some isolates showed some novel mutations effect of which we are unable to explain at this time. It is imperative to continue monitoring of these viruses for identification of potential variants of high virulence as well as drug resistance.

PROJECT TITLE: Specific mutations in the large S gene of Hepatitis B Virus: Characterization and Impact on Disease Progression

RAC Approval #: 2150008

Source of Funding: KACST

DESCRIPTION: The aim of this project was to investigate the prevalence and pattern of large S gene mutations and their clinical significance in different categories of infections among Saudi patients. The analysis showed that six amino acid mutations significantly associated with the progression of HBV infection were identified. These included, a significant mutation (p=0.017) at position 75 with threonine replaced by glutamine (T75Q) present in 93.78% of inactive carriers as compared to 85.83% of the combined group patients (active+cirrhosis+HCC) (Figure 2 and table 5). Histidine is mutated to glutamine at position 117 (H117Q) in 0.52% of inactive carriers and in 5.51% of the patients in the combined group (p=0.007). 20.47% of patients from the combined group with advanced HBV infection had phenylalanine to leucine mutation at position 130 (F130L) while only 10.36% of inactive carriers had this mutation (p=0.012). At position 205 mutation of leucine to arginine (L205R) is present in 4.72% of combined group patients whereas only 0.52% of inactive carriers had this significant mutation (p=0.017). Alanine at position 208 is mutated to threonine (A208T) in 85.49% of inactive carriers and in 64.57% of the combined group patients (p<0.0001). The mutation at position 367 of asparagine to serine (N370S) was significant (p=0.011) and was found in 70.08% of the combined patient group (active+cirrhosis+HCC) as compared to 55.96% of inactive carriers individuals. In conclusion, mutational analysis of the large S gene of HBV could be used as a useful tool to predict progression of liver diseases associated with HBV infection.

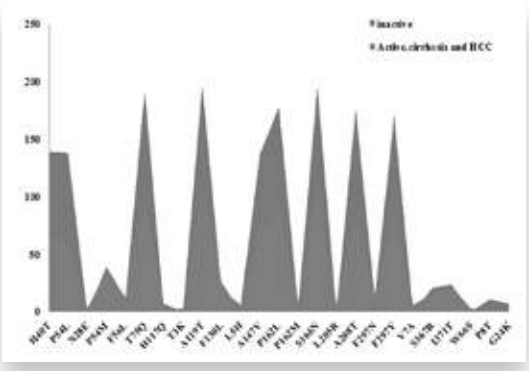

Figure 2. Mutations that significantly differ in frequency between inactive vs. active, cirrhosis and HCC groups.

Table 4. Amino acid variations within the large S gene of HBV patients.

	Mean	Std. Deviation	p-value
Inactive	86.37	79.99	0.009
Active, cirrhosis and HCC	57.16	51.42	

PROJECT TITLE: Modeling of Immunosuppression and Clinical Trials In Renal Transplantation
RAC# 2111-005
Source of Funding: KACST

DESCRIPTION: Here, we are aiming at establishing a first-of-its-kind, comprehensive mathematical model for the evaluation of immunosuppressive strategies that integrates clinical, virological and immunological data that can provide a unifying algorithm to predict the degree of immune suppression. In a future extension of this project, this model will then be empirically validated using a prospective clinical trial in which the predictive value of this model will be used to guide treatment decisions. Overall, this project (1) focuses on a key aspect of organ transplantation, (2) offers clear perspectives for translational medicine to improve routine clinical care, and (3) provides an important example for an international collaborative study between two world-renowned institutions.

PROJECT TITLE: Prediction of Invasive Fungal Infection in BMT Patients
RAC# 2140-034
Source of Funding: KFSH&RC

DESCRIPTION: Here, we aim to establishing a first-of-its-kind, diagnostic strategy to measure an individual patient's fungal immune reserve. The proposed scientific strategy in this study uses a personalized approach, where immunological data required for an immune reserve assessment would be derived from each individual patients using *ex vivo* assays. Algorithms based on cytokine profiling as well as whole genome expression from circulating monocytes will be used to predict the risk of invasive fungal disease in BMT patients. This study proposal recruits patients with defined clinical phenotypes recruiting BMT patients with and without invasive fungal infection. In a future extension of this project, the diagnostic variables collected here will be used to develop a predictive algorithm to be validated in a prospective clinical trial of invasive fungal infection in the BMT population. Overall, this project (1) focuses on the known high mortality, high risk infection of invasive fungal disease in the leukemic and BMT population, (2) offers clear perspectives for personalized translational medicine with aim to improve routine clinical care, and (3) provides an important example for an international collaborative study between two world-renowned institutions.

PROJECT TITLE: Functional Properties of Dendritic Cells in Saudi HIV-1 Elite Controllers
RAC# 2111-001
Source of Funding: KACST

DESCRIPTION: Elite controllers represent a small proportion of HIV-1 infected persons with undetectable viremia in the absence of antiretroviral therapy, and these patients have moved into the center of current efforts to identify correlates of immune protection against HIV-11. Most prior studies have focused on the analysis of T- and B- cell responses in these patients, however, is now clear that such classical adaptive immune responses alone are not the major reason for undetectable viremia in these patients2. Dendritic cells, a key element of the innate immune system, play a central role in structuring host immunity3,

but functional characteristics of these cells in elite controllers are unclear. Here, the applicant proposes to conduct a detailed analysis of dendritic cells in elite controllers by focusing on two specific aims, namely (1) analysis of phenotypic and functional properties of myeloid and plasmacytoid dendritic cells in HIV-1 infection, and (2) assessment of the functional regulation of dendritic cells from elite controllers by Leukocyte immunoglobulin Like receptors (LILR).

PROJECT TITLE: Investigating the Possible Role of the Mutated Gene(s) in Aicardi–Goutieres Syndrome in HIV Infection
RAC# 2130-035
Source of Funding: KFSH&RC

DESCRIPTION: Aicardi–Goutiere syndrome (AGS) is a hereditary neurodegenerative disorder characterized mainly by early onset progressive encephalopathy, concomitant with an increase in interferon-α (IFN-α) levels in the cerebrospinal fluid. AGS was initially mistaken for intrauterine viral infections, but is now attributed to a lack of adequate processing of cellular nucleic acid debris, which culminates in the perpetual trigger of the innate and acquired immune responses. Although the exact mechanisms governing AGS are not fully understood, recent studies have described four proteins found mutated in AGS. A few investigations have now uncovered that AGS is tightly linked with the predisposition to other autoimmune disorders such as familial chilblain lupus and systemic lupus erythematosus. Moreover, at least two of the proteins mutated in AGS, namely TREX1 and SAMHD1, also seem to have antagonistic roles in safeguarding humans from human immunodeficiency virus (HIV) infections. Studying the mechanisms underlying the different mutated genes within the AGS patients will shed light on a better understanding of the innate immune response against retroviruses and assist in the future development of more effective anti-HIV interventions. Knowledge of these proteins, mutations and the different pathways that they are involved with could be useful not only for AGS but also for other IFN-α-related pathologies such HIV infections. In this project we propose to investigate this intriguing genetic candidates (AGS) to better understand AGS that might help us to further findings for a better treatment not only for some autoimmune disorders but also possibly for patients suffering from HIV infections, too. Therefore we aim to (1) investigate the relation and the roles of these the mutated gene(s) in the suppression of retroviral infections, and to elucidate the immune dysfunctions, those are associated with the identified mutated gene(s).

PROJECT TITLE: The Role of SAMHD1 in HIV-2 (Vpx) Gene Expression and its Relation to HIV-2 Pathogenesis
RAC# 2130-003
Source of Funding: KACST

DESCRIPTION: HIV is Lentivirus that attacks the immune systems and cause disease known as AIDS. HIV/AIDS is considered as pandemic infection by the World Health Organization. Vpx gene exists in HIV-2 genome only and it has been recently shown that it can induce proteasomal degradation of SAMHD1, which will lead to the increase of HIV infection in non-permissive cells (e.g. DCs). We aim to produce for the first time a Vpx recombinant DNA from an HIV-2 patient and therefore, study the role of SAMHD1 expression and its effect on HIV-2 (VPX gene) product. It is expected that studying the mechanisms underlying SAMHD1-mediated HIV restriction will shed light on the innate immune response against retroviruses and assist in the future development of more effective anti-HIV interventions.

PROJECT TITLE: Understanding the Role of Innate Immune Humoral Factor in HIV-1
RAC# 2140-032
Source of Funding: KFSH&RC

DESCRIPTION: HIV-1 main cellular target involves CD4+ T cells, while antigen presenting cells such as macrophages and dendritic cells act as viral reservoirs. Although a number of studies have focused on understanding HIV-1-T cell interaction which impact upon cell-mediated immunity directly, the role of innate immune system, especially soluble pattern recognition molecules, have recently been recognized. For instance, we have recently shown that Surfactant Protein, SP-D, a member of the collectin family and a pattern recognition protein which is secreted by mucosal epithelial cells, has an important role in innate immune defense against HIV-1. In this project, we wish to examine interaction of three key complement proteins: C1q, factor H and properdin, and examine whether these three soluble factors can interfere with HIV-1: target cell interaction. C1q is the first subcomponent of the classical pathway of the complement system which is known to interact with HIV-1 but the ability of its HIV-1 binding globular domain alone to modulate HIV-1 infection is not known. Properdin and factor H are two key regulatory proteins having opposite functions in the alternative complement pathway. Properdin up-regulates the alternative pathway by stabilizing the C3bBb complex, whereas factor H down-regulates the pathway by promoting proteolytic degradation of C3b. Recent studies have revealed that C1q, factor H and properdin can be produced locally at the site of infection and inflammation by immune cells and they can have functions which do not require their involvement in complement activation. We have recently shown that both factor H and properdin interact with influenza A virus (IAV) and suppress infection and pro-inflammatory immune response. This study should highlight the importance of soluble factors in HIV-1 pathogenesis with potential to develop immunotherapy to inhibit viral entry and immune activation in acute HIV infection.

PROJECT TITLE: Lymphoma in HIV-Infected Patients in Saudi Arabia: Prevalence, Incidence and Genetic Polymorphism
RAC# 2140-034
Source of Funding: KFSH&RC

DESCRIPTION: HIV infection is well-known to impair cellular immunity and cause malignancies AIDS-related lymphoma was reported in 28% of HIV infected patients with an incidence rate of 1.18 per 100 patient-years. On the other hand, lymphoma is the third registered cancer among Saudis between 1975 and 2012 reaching 7.5% of all cancers. Saudi Arabia reported around 4000 cases of HIV infection among the citizens till 2012. Some genetic mutations were linked to some types of NHL in HIV patients worldwide. However, this was never been tested in Saudi patients before. We aim to determine the genetic polymorphism of lymphoma in HIV patients in Saudi Arabia. This is a retrospective cohort study in all HIV patients with lymphoma at KFSH&RC in Saudi Arabia in the period between 1984 and 2014. Tissue blocks from HIV-infected lymphoma patients will be used to determine any genetic polymorphisms. We expect to find some genetic predisposition of lymphoma in HIV patients in Saudi Arabia which could be different than the worldwide cases. We aim to determine the genetic polymorphism of lymphoma in an HIV infected cohort of patients in Saudi Arabia. We believe determining the gene mutations and genetic polymorphism associated to lymphoma in HIV patients could greatly impact future therapy options and determining prognosis. Gene targeted therapy is already growing in many types of leukemia but we could also find a linked gene to each specific subtype of lymphoma. That

indeed will affect future strategies in targeted treatment and even determining prognosis of each.

PROJECT TITLE: Development of Anti-MERs CoVirus Hyper Immune Product
RAC# 2140-025
Source of Funding: KFSH&RC

DESCRIPTION: Middle East Respiratory Syndrome-Corona Virus (MERS-CoV) is a deadly respiratory virus currently endemic in Saudi Arabia and spreading into neighboring Middle Eastern countries, Asia Pacific, Europe and the United States. Although many laboratories around the world are actively working on finding a solution to limit its spreading, there are currently no cure or vaccine to this deadly virus. We aim to provide an accelerated development path for a hyperimmune for MERS-CoV, through purifying MERS-CoV IVIG from plasma drawn from prescreened, high-titer convalescent MERS-CoV donors. Hyperimmune immunoglobulin products provide a key therapeutic for passive immunization of populations at risk and may reduce the impact of MERS-CoV to alleviate the burden imposed on the client by this disease and its ramifications.

PROJECT TITLE: Genome Sequencing to Characterize Unknown Mutations and Identify the Phylogeny of Unknown Drug Resistant *Mycobacterium Tuberculosis* Strains Causing an On Going Transmission in Saudi Arabia
RAC# 2130020
Source of Funding: KACST

DESCRIPTION: Drug resistant tuberculosis (TB) is the major concern of TB control globally and Saudi Arabia also faces a considerable threat from drug resistant TB. Annual surveillance reports on drug resistant tuberculosis showed 4% multidrug resistant TB (MDRTB) and 23% any drug resistance. On other hand 3-6% of *Mycobacterium tuberculosis* (MTB) isolates transmitting in the country belonged to undefined clades. Interestingly, the ongoing transmission of undefined clades of MTB including drug resistant strains makes the scene worst in TB control programs. In addition, there are several unknown mutations conferring anti-TB drug resistance reported largely in the country, which could not be detected by the current diagnostic platforms. This restricts the rapid identification of certain drug resistant isolates based on molecular diagnosis. A further point of consideration is that the magnitude of MDRTB transmission is not clearly defined in the country. Therefore this project is aimed to trace the undefined clades of MTB causing ongoing transmission, drug resistance causing unknown mutations and the transmission dynamics of multidrug drug resistant TB from a national level collection of MTB isolates. The "undefined TB clades" will be defined by screening of isolates with the most discriminative genotyping methods of MTB, 24 loci MIRU-VNTR typing and spoligotyping. Whole genome sequencing of isolates enrolled as "undefined clades" and with "undefined mutations" will be carried out to streamline the final genetic profiling. The key focus of the study is that, if significant volume of new mutations is established, a new kit for drug resistant TB detection would be designed.

PROJECT TITLE: First National Surveillance and Genetic Diversity Study on Emerging Non-tuberculous Mycobacterial Infections in Saudi Arabia
RAC# 2130021
Source of Funding: KACST

DESCRIPTION: Non Tuberculous Mycobacteria (NTM) is usually saprophytes found in natural sources. Almost 150 species are officially identified until 2015, and ~50 of them are found to be pathogenic to human. Human to human transmission of NTM's are rarely reported, thus the pathological

consideration of these mycobacterial group was limited before. Currently emergence of NTM's causing infections became a serious threat for public health globally and Saudi Arabia is not an exception. There are no national level prevalence data on NTM infections in Saudi Arabia until today. Recent reports showed a higher prevalence of various NTM species (10% of total mycobacterial diseases reported annually) causing pulmonary and extrapulmonary infections majorly among the Saudi population. Interestingly, a new species of NTM-*Mycobacterium riyadhense* was also isolated from Riyadh recently. One of our recent reports represented a higher diversity of clinically relevant NTM's with 13 different species causing pulmonary and extrapulmonary diseases. Increase in the rates of immunosuppressive illness and treatment provide a higher importance for the flaring of NTM disease. In addition the country has the highest consanguinity rates globally which led to several immune deficiencies that reported with susceptibilities to mycobacterial diseases. Keeping all these facts, the project is designed to extensively evaluate the epidemiology of NTM disease in different regions of the country, species diversity of NTM's, genetic diversity and drug resistance pattern of common NTM species. This is the first national surveillance study of NTM's to be conducted in GCC states and mostly in Asia.

PROJECT TITLE: Genotyping *Mycobacterium Tuberculosis* from Patients with Extra-pulmonary Tuberculosis
RAC# 2090018
Source of Funding: KACST

DESCRIPTION: Globally Extrapulmonary tuberculosis (EPTB) is a significant component of all tuberculosis burdens. Saudi Arabia reports with a relatively higher rate of EPTB compared to any other country globally which is around 30% of the total notified tuberculosis cases annually. EPTB is difficult to diagnose and received less priority than pulmonary tuberculosis because of its low potential of human to human transmission. The changes in populations, health care services, and possibly the pathogen have contributed to the increase in EPTB, locally and globally. There is scarcity of data on molecular epidemiology of EPTB globally and particularly in the Kingdom. Therefore this study is focused mainly to genotype the isolates of *Mycobacterium tuberculosis* (MTB) causing EPTB in Saudi and non-Saudi populations. It is a multicenter study participating King Faisal Specialist Hospital and Research Centre, Riyadh, King Abdulaziz Medical City- National Guard Health Services, Riyadh, King Fahad Medical City Riyadh and Prince Sultan Military Medical City Riyadh. All the isolates enrolled to the study will be subjected to 24 loci MIRU-VNTR typing and spoligotyping. The molecular signatures of the isolates will be assessed with site of infection and then compared to the existing profiles from local and international repositories. A comparison of lineages causing EPTB and pulmonary TB in the country will be carried out in detail. The outcome will lead to streamline the modern selectiveness hypothesis of specific MTB clades to site of infection and finding the clades specific to the local population can create a platform for future research on personalized TB medicine.

PROJECT TITLE: Detecting *Mycobacterium Tuberculosis* by Molecular Techniques in Transplanted Organs
RAC# 2130031
Source of Funding: KACST

DESCRIPTION: It is estimated that one-third of the world's population carries latent tuberculosis (TB), and millions of reactivated TB cases are predicted in the coming years. Not all patients infected with *Mycobacterium tuberculosis* progress to active disease, but majority remain with latent TB infection. However, up to ten percent may progress to active infection. Although TB is

uncommon among transplant recipients, the risk of TB among solid organ

transplant recipients is 50-fold more compared with general population leading to the higher mortality rate among these patients up to 40 percent. There are several ways a transplant recipient may develop active TB infection. Most frequently it is due to re-activation of latent *Mycobacterium tuberculosis* infection after initiation of immunosuppressive therapy. The organ recipient may also present with primary TB infection caused by exposure to infectious air droplets from an infected individual. Least commonly, transmission of the infection is through organs inadvertently transplanted from individuals infected with *Mycobacterium tuberculosis*. The key objective of the study is to test the harvested organs for transplantations particularly livers and kidneys for *Mycobacterium tuberculosis* DNA by molecular techniques such PCR in Situ Hybridization. The DNA possible to extract from the organ tissues will be subjected to genotyping methods to find the specific lineages. Furthermore, identify the implications of positive M. tuberculosis DNA in transplanted organs in the recipient host. A cross match will be carried out to both cases (recipient and donor), then a decision may be reached to conclude whether the donor gave the TB to the recipient. Followed up and later on identifying any risk will lead to an early chemotherapy to prevent the establishment of active disease.

PROJECT TITLE: Human Papillomavirus (HPV) Viral Load and E6/E7 mRNA Expression as Predictive Markers for the Development of Cervical Carcinoma

RAC# 2130 033

Source of Funding: KACST

DESCRIPTION: The overall goal of the proposed study is to determine whether the presence of high HPV viral load and E6/E7 mRNA expression correlate with disease progression. To this end, we have recruited over 500 patients who attended the Primary Care Clinic or the Obstetrics and Gynecology Clinic at King Faisal Specialist Hospital and Research Centre (KFSH&RC) in Riyadh, Saudi Arabia, for routine cervical examinations. Cervical specimens from those women were examined for normal and abnormal cytology, and the stages of abnormal cytology were scored according to the Bethesda classification. HPV DNA testing was done using PCR amplification of the L1 gene and genotype HPV-positive results by GenoFlow assay. Questionnaires that include sociodemographic and sexual behavior factors were filled in by the enrolled participants and were collected by a clinical coordinator during the participants' clinical visits. Our results so far showed that approximately 17% of the women were HPV-positive. The most commonly detected HPV types were HPV-18 (34%) and HPV-16 (19%), with multiple infections detected in 10% of positive specimens (Figure 3). Moreover, 73% of the women tested were Saudi nationals. Nearly 50% were under 40 years old (range, 22–80 years; mean ± SD, 41.20 ± 10.43 years) (Figure 4). Multivariate analyses revealed that smoking and multiple partners were significant risk factors for HPV infection ($P < 0.01$) (Table 5–6).

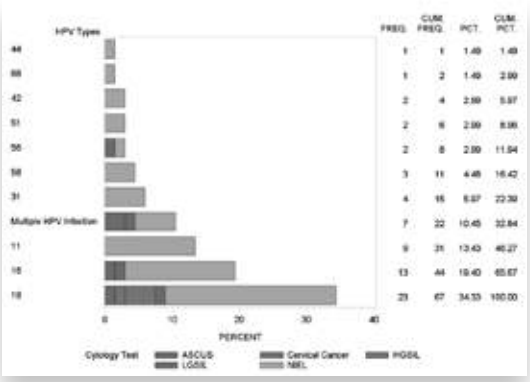

Figure 3. HPV genotypes and cytology results.

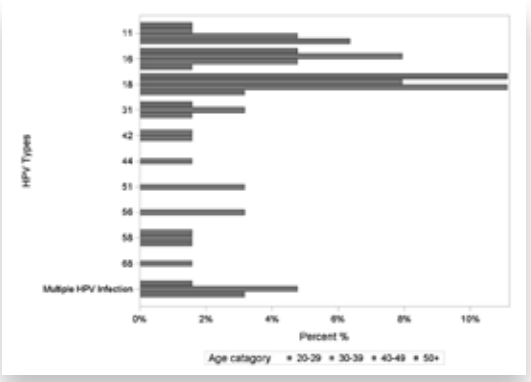

Figure 4. HPV genotypes and age categories.

Table 5. Sexual behavior characteristics of the study cohort.

	HPV positive (n=67)	HPV negative (n=377)	Total % (N=400)	x2 (df)
AGE AT FIRST INTERCOURSE				
Mean (SD)	22.0 (4.89)	21.42 (4.97)		t-value = 0.74
LIFETIME SEXUAL PARTNERS				8.8 (2)**
One (352)	16.0 (56)	84.0 (298)	88.4 (354)	
Two (30)	13.3 (4)	86.7 (26)	7.5 (30)	
3 or more (16)	44.0 (7)	56.0 (9)	4.0 (16)	
Number of sexual partners Mean (SD)	1.3 (0.76)	1.14 (0.48)		t-value = 1.6
Number of children, Mean (SD)	5.44 (2.48)	4.79 (2.56)		t-value = 1.75
CONTRACEPTIVE USE				0.38 (1)
Yes	16.0 (46)	84.0 (241)	72.0 (287)	
No	19.0 (21)	81.0 (92)	28.0 (113)	
CONTRACEPTION TYPE				3.5 (3)
None used	19.0 (21)	81.0 (92)	28.0 (113)	
Condom	0.0 (0)	100.0 (5)	1.3 (5)	
IUD	14.0 (24)	86.0 (151)	44.0 (175)	
Oral pills	21.0 (22)	79.0 (85)	27.0 (107)	
CONTRACEPTION USE DURATION IN MONTHS, MEAN (SD)	50.41 (50.22)	47.58 (35.57)		t-value = 0.46

**P < 0.01

Table 6. Sociodemographic characteristics of the study cohort.

		HPV positive 16.8% (n = 67)	HPV negative 83.3% (n = 333)	Total % (N = 400)	x^2 (df)
		% (n)	% (n)	% (n)	
AGE					5.8 (4)
20-29 (65)		20.0 (13)	80.0 (52)	16.3 (65)	
30-39 (119)		17.0 (20)	83.0 (99)	30.0 (119)	
40-49 (123)		17.0 (21)	83.0 (102)	31.0 (123)	
50+ (93)		13.0 (13)	86.0 (80)	23.7 (93)	
	Mean age (SD)	40.3 (10.67)	41.43 (10.38)		t-value = 1.002
RELIGION					2.7 (1)
Christian (43)		25.6 (11)	74.4 (32)	11.0 (43)	
Islam (357)		16.0 (56)	84.0 (301)	89.0 (357)	
NATIONALITY					0.28 (1)
Saudi (291)		16.0 (47)	84.0 (244)	73.0 (291)	
Non-Saudi (109)		18.0 (20)	82.0 (89)	27.0 (109)	
EDUCATION					1.6 (3)
Primary (28)		11.0 (3)	89.0 (25)	7.0 (28)	
Intermediate (41)		19.5 (8)	80.5 (33)	10.0 (41)	
Secondary (149)		19.0 (28)	81.0 (121)	37.0 (149)	
Higher (181)		15.5 (28)	84.5 (153)	45.0 (181)	
ANNUAL HOUSEHOLD INCOME (USD)(REF: >5,333.40)					
<800.01 (34)		20.0 (10)	71.0 (24)	9.0 (34)	4.1 (3)
1,066.68-2,400.03 (31)		13.0 (4)	87.0 (27)	8.0 (31)	
2,666.70-5,333.40 (161)		16.0 (26)	(84.0 (135)	42.0 (161)	
>+5,333.40 (158)		17.0 (27)	83.0 (131)	41.0 (158)	
MARITAL STATUS					0.72 (2)
Married (350)		16.3 (57)	83.7 (293)	87.5 (350)	
Divorced (38)		18.4 (7)	81.6 (31)	9.5 (38)	
Widowed (12)		25.0 (3)	75.0 (9)	3.0 (12)	
SMOKING STATUS					
Yes (119)		27.0 (32)	73.0 (87)	30.0 (119)	12.5 (1)***
No (281)		12.5 (35)	87.5 (246)	70.0 (281)	

***P < 0.001

PROJECT TITLE: The Prognostic Impact of Human Papillomavirus (HPV) Genotypes on Cervical Dysplasia and Cancer in a Saudi population. A retrospective Cross-sectional Study

RAC #: 2150 001

Source of Funding: KFSH&RC

DESCRIPTION: The main goals of the proposed study are to examine the correlation between HPV presence, p16 overexpression, and disease progression in a hospital-based cohort (i.e., KFSH&RC) utilizing archived paraffin-embedded tissues (from 2004 to 2014), and analyze the overall survival rate (OS) of HPV-infected patients. Our results showed that out of 267 archived biopsies, 29 % were

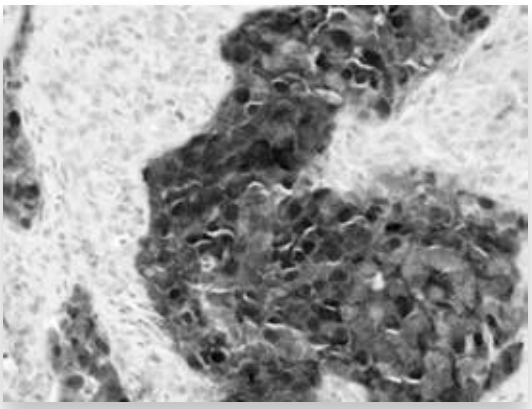

Figure 5. P16 expression in Squamous Cell Carcinoma (Immunohistochemistry, H&E stain).

Table 7. Demographic characteristics of the study cohort.

	HPV positive 28.84% (n = 77)	HPV negative 71.16% (n = 190)	Total % (N = 267)	x2 (df)
	% (n)	% (n)	% (n)	
AGE				0.7690 (3)
20-29 (2)	0 (0)	100.0 (2)	2.74 (2)	
30-39 (22)	27.27 (6)	72.73 (16)	30.14 (119)	
40-49 (20)	25.00 (5)	75.00 (15)	27.40 (123)	
50+ (29)	27.59 (8)	72.41 (21)	39.73 (93)	
Mean age (SD)	45.74 (10.81)	46.46(12.69)		t-value = 0.24
RELIGION				0.85 (1)
Christian (8)	12.50 (1)	87.50 (7)	10.96 (43)	
Islam (65)	27.69 (18)	72.31 (47)	89.04 (65)	
NATIONALITY				0.6536 (1)
Saudi (61)	27.87 (17)	72.13(44)	83.56(61)	
Non Saudi (12)	16.67 (2)	83.33(10)	16.44(12)	
MARITAL STATUS				
Married (59)	23.73 (14)	76.27 (45)	80.82 (59)	
Divorced (3)	33.33 (1)	66.67 (2)	4.11 (3)	
Widowed (6)	50.00 (3)	50.00 (3)	8.22 (6)	
Single (5)	20.00(1)	80.00(4)	6.85(5)	

HPV positive. The statistical analysis showed no significant association between HPV positivity and demographical data (Age category, marital status, Religion and Nationality) (Table 7). P16 immunostaining was performed on 120 slides so far and the results showed that 40% were p16 positive indicating an oncogenic activity of HR-HPV (Figure 5).

PROJECT TITLE: Epidemiological and Demographic Characteristics of MERS CoV Cases from 2012–Present
RAC#: 2150 026
Source of Funding: KFSH&RC

DESCRIPTION: To distinguish outbreak from non-outbreak cases, we examined epidemiologic, demographic, and clinical characteristics of Middle East respiratory syndrome (MERS) CoV contracted in Saudi Arabia from September 2012 through October 2015 using data acquired from the Saudi Ministry of Health (Figure 6). Using univariate and descriptive statistical analyses, we determined that 1250 patients (aged 0 to 109 years; mean, 50.825 years) were reported infected with MERS coronavirus (CoV). Among all reported cases, two-thirds were diagnosed in men while 22% were in healthcare workers. Nosocomial infections comprised one-third of all cases, but they occurred more frequently in outbreak than non-outbreak cases ($p<0.001$), suggesting that nosocomial infections fueled MERS outbreaks (Figure 7). Patients contracting MERS during an outbreak were significantly more likely to die of MERS ($p<0.001$) (Table 8). Given that Saudi Arabia is a worldwide religious travel destination, localized outbreaks may have marked global implications, and effective outbreak preventive measures are needed.

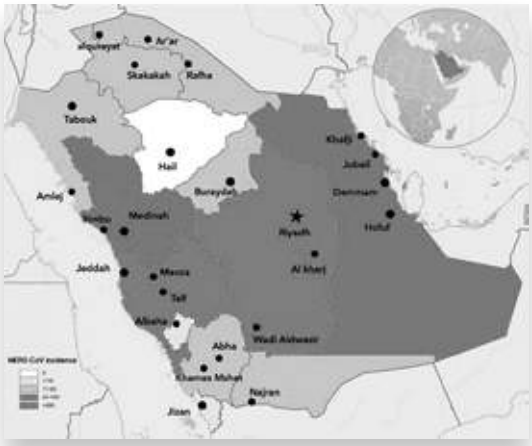

Figure 6. Incidence of MERS coronavirus infections (1250 confirmed cases) across the Kingdom of Saudi Arabia.

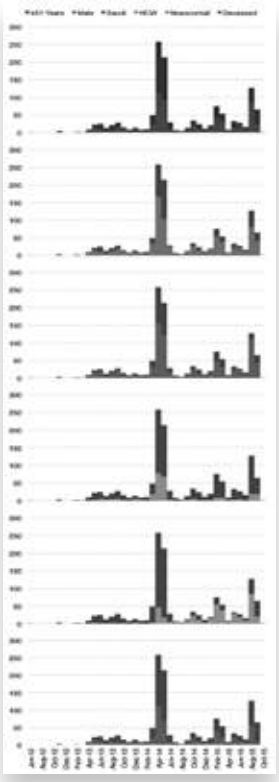

Figure 7. Epidemiologic curve showing the number of cases of MERS-CoV infection and various patient characteristics in the Kingdom of Saudi Arabia by month and year of confirmation. HCW, healthcare worker.

Table 8. Patient characteristics in Middle East respiratory syndrome infection cases reported in the Kingdom of Saudi Arabia from 2012 to 2015.

Demographic characteristics (n)	Frequency	Percentage
AGE IN YEARS (1244)		
0-10	41	3.30
11-25	63	8.36
26-39	292	31.83
40-109	848	68.17
GENDER (1246)		
Female	439	35.23
Male	807	64.77
OCCUPATIONAL STATUS (172)		
Employed	22	12.79
Unemployed	40	23.26
Retired	31	21.51
Private	37	18.02
Other	42	24.42
MAIN REASON FOR TESTING (1247)		
Healthcare worker	249	19.97
Household	138	11.07
Suspect	860	68.97
HEALTHCARE WORKER (1244)		
Yes	275	22.11
No	969	77.89
DOES THE PATIENT RAISE CAMELS? (205)		
Yes	29	14.15
No	176	85.85
DURING THE 14 DAYS BEFORE THE PATIENT BECAME SICK, DID HE/SHE TRAVEL OUTSIDE OR INSIDE SAUDI ARABIA? (205)		
Yes	195	95.12
No	10	4.88
WAS THE PATIENT HOSPITALIZED WHEN A POSITIVE RESULT WAS OBTAINED? (450)		
Yes	413	91.78
No	37	8.22
DID THE PATIENT VISIT ANY HEALTHCARE FACILITIES DURING THE 14 DAYS BEFORE ONSET OF SYMPTOMS? (245)		
Yes	98	40
No	109	44.49
Unknown	38	15.51
DOES THE PATIENT SMOKE? (205)		
Yes	36	17.56
No	169	82.44

SELECTED ACHIEVEMENTS

- Formation of scientific collaboration nationally, regionally and internationally
- Development of HIV-2 viral load assay using a real-time RT-PCR assay
- Graduate degrees supervisors and examiners in various national, regional and international universities
- The role of polymorphism in IL28B gene in hepatitis B virus infection in Saudi patients was elucidated
- Revealing the role of host response to hepatitis C virus
- Genetic analysis of H5N1 and H1N1 virus that circulated in Saudi Arabia was revealed
- Molecular characterization of bacteria-causing nosocomial infection
- Add hoc reviewers for several scientific journals, KACST and MAARIFAH
- Launching of the REDcap database for KFSH&RC-RUH
- Establishment of the initial phase of HIV/AIDS Awareness Campaign
- Invited speakers and/or session chairs at various conferences, meetings and symposia that were carried out nationally, regionally and internationally
- Training of over 20 Saudi college graduates
- Obtaining the "L' OREAL-UNESCO Award For Women In Science in the MENA Region"
- Advisory role to the National AIDS Program of EMRO-WHO

LIST OF SELECTED PEER-REVIEWED PUBLICATIONS

- Al-Qahtani A, Al-Anazi M, Abdo AA, Sanai FM, Al-Hamoudi W, Alswat KA, Al-Ashgar HI, Khan MQ, Albenmousa A, Khalaf N, Viswan N, Al-Ahdal MN (2015) Correlation between genetic variations and serum level of interleukin 28B with virus genotypes and disease progression in chronic hepatitis C virus infection. *Journal of Immunology Research* 2015:768470, doi: 10.1155/2015/768470. http://www.ncbi.nlm.nih.gov/pubmed/25811035
- Alhamlan FS, Al-Qahtani AA, Al-Ahdal MN (2015) Current studies on human papillomavirus in Saudi Arabia. *Journal of Infection in Developing Countries* 9(6):571-576. http://www.ncbi.nlm.nih.gov/pubmed/26142665
- Al Hajoj S, Shoukri M, Memish Z, Al Hakeem R, AlRabiah F, Varghese B (2015) Exploring the sociodemographic and clinical features of extrapulmonary tuberculosis in Saudi Arabia. *PLoS One* 10(2):e0101667. doi: 10.1371/journal.pone.0101667. http://www.ncbi.nlm.nih.gov/pubmed/25647300
- Alhamlan FS, Al-Qahtani AA, Al-Ahdal MN (2015) Recommended advanced techniques for waterborne pathogen detection in developing countries. *Journal of Infection in Developing Countries* 9(2):128-135. doi: 10.3855/jidc.6101. http://www.ncbi.nlm.nih.gov/pubmed/25699486
- Al-Qahtani AA, Mubin M, Almajhdi FN, Alarifi S, Dela Cruz DM, Rehman MS, Ismail MM, Ahmed N, Al-Blowi MH, Khalak H, Al-Ahdal MN (2015) Characterization of H5N1 influenza A virus that caused the first highly pathogenic avian influenza outbreak in Saudi Arabia. *Journal of Infection in Developing Countries* 9(11):1210-1219. http://www.ncbi.nlm.nih.gov/pubmed/26623630.
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- AbuOdeh R, Al-Mawlawi N, Al-Qahtani AA, Bohol MF, Al-Ahdal MN, Hasan HA, AbuOdeh L, Nasrallah GK (2015) Detection and

genotyping of torque teno virus (TTV) in healthy blood donors and patients infected with HBV or HCV in Qatar. *Journal of Medical Virology* 87(7):1184-1191. http://www.ncbi.nlm.nih.gov/pubmed/25676255

- Goulidaki N, Alarifi S, Alkahtani SH, Al-Qahtani A, Spandidos DA, Stournaras C, Sourvinos G (2015) RhoB is a component of the human cytomegalovirus assembly complex and is required for efficient viral production. *Cell Cycle* 14(17):2748-2763. http://www.ncbi.nlm.nih.gov/pubmed/26114383
- Lopes BS, Al-Agamy MH, Ismail MA, Shibl AM, Al-Qahtani AA, Al-Ahdal MN, Forbes KJ (2015) The transferability of blaOXA-23 gene in multidrug-resistant Acinetobacter baumannii isolates from Saudi Arabia and Egypt. *International Journal of Medical Microbiology* 305(6):581-588. http://www.ncbi.nlm.nih.gov/pubmed/26253451
- Sotiriadis G, Dodagatta-Marri E, Kouser L, Alhamlan FS, Kishore U, Karteris E (2015) Surfactant proteins SP-A and SP-D modulate uterine contractile events in ULTR Myometrial cell line. *PLoS One* 10(12):e0143379. doi: 10.1371/journal.pone.0143379. http://www.ncbi.nlm.nih.gov/pubmed/26641881
- Al-Sultan AA, Evans BA, Aboulmagd E, Al-Qahtani AA, Bohol MF, Al-Ahdal MN, Opazo AF, Amyes SG (2015) Dissemination of multiple carbapenem-resistant clones of Acinetobacter baumannii in the Eastern District of Saudi Arabia. *Frontiers in Microbiology* 6:634. doi: 10.3389/fmicb.2015.00634. http://www.ncbi.nlm.nih.gov/pubmed/26191044
- Alhamlan FS, Al-Ahdal MN, Khalaf NZ, Abdo AA, Sanai FM, Al-Ashgar HI, ElHefnawi M, Zaid A, Al-Qahtani AA (2014) Genetic variability of the core protein in hepatitis C virus genotype 4 in Saudi Arabian patients and its implication on pegylated interferon and ribavirin therapy. *Journal of Translational Medicine* 12:91. doi: 10.1186/1479-5876-12-91. http://www.ncbi.nlm.nih.gov/pubmed/24708767
- Al-Mozaini MA, Mansour MK, Al-Hokail AA, Mohmed MA, Bin Daham MA, Al-Abdely HM, Frayha HH, Al-Rabiah FA, Alhajjar SH, Keshavjee S, Adra CN, Alrajhi AA (2014) HIV-care outcome in Saudi Arabia; a longitudinal cohort. *Journal of AIDS and Clinical Research* 5(11): pii370. http://www.ncbi.nlm.nih.gov/pubmed/25750760
- Pandit H, Gopal S, Sonawani A, Yadav AK, Qaseem AS, Warke H, Patil A, Gajbhiye R, Kulkarni V, Al-Mozaini MA, Idicula-Thomas S, Kishore U, Madan T (2014) Surfactant protein D inhibits HIV-1 infection of target cells via interference with gp120-CD4 interaction and modulates pro-inflammatory cytokine production. *Plos One* 9(7):e102395. doi: 10.1371/journal.pone.0102395. http://www.ncbi.nlm.nih.gov/pubmed/25036364
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MOLECULAR BIOMEDICINE PROGRAM

MOLECULAR BIOMEDICINE PROGRAM

DIRECTOR

Khalid S. Abu Khabar, PhD

ADMINISTRATIVE SUPPORT

Marisol Sobreviga

STAFF

Edward Hitti, PhD *Scientist*
Fahad Al-Zoghaibi *Scientist*
Norah Al-Souibani, PhD *Post-Doctoral Fellow*
Tala Bakheet, PhD *Post-Doctoral Felllow*
Walid Moghrabi, MSc *Technical Specialist*
Latifa Al-Haj, MSc *Technical Specialist*
Maha Al-Ghamdi, MSc *Research Assistant*
Wijdan Al-Ahmadi, BSc *Research Assistant*
Maher Al-Saif, BSc *Research Assistant*
Lina Omar Mahnoud, BSc *Research Technician*
Suhad Al-Yahya, BSc *Research Technician*
Mosaab Doubi *Research Technician*
Nada Al-Mutairi, MSc *Research Technician*
Rana Kattan *Research Technician (Grant)*

THE MOLECULAR BIOMEDICINE PROGRAM OBJECTIVE IS TO investigate molecular mechanisms of diseases and develop necessary tools with potential translational outcome in therapy or in medical biotechnology. The program currently focuses on a medically important family of genes associated with regulating mRNA stability and translation which are perturbed as a result of disease. The program has a unique and internationally well-known research platform which is applicable to several chronic disease conditions that impact the health care in Saudi Arabia including inflammatory, infectious, and cardiovascular diseases, and cancer.

Functional Sections: Interferon and Cytokines; Disease System Biology; Translational Biotechnology; Computational Biology.

PROJECTS

RAC

- AU-Rich Element Interactome in Cancer. A systematic analysis of AU-Rich mRNA expression across different types of cancer in an attempt to discover significant expression patterns and their functional relationship with expression levels of the RNA binding proteins Tristetraprolin (TTP) and Human Antigen R (HuR). The findings will have a significant impact on modulation of key cancer-promoting pathways and subsequently high therapeutic potential.

KACST FUNDED

- Post-transcriptional control of gene expression: screening of drug-like compounds and modulation in cancer cells. Highly recommended by the American Association for the Advancement of Science (AAAS) review. SAR 1,800,250.00 was granted for this project.

  This project aims for screening for drugs that are capable of reducing the expression of AU-rich element containing genes in cancer. This unique pharmacological approach was highly recommended from AAAS for the following reasons. (i) ARE-mRNAs should, by default, be expressed at very low levels in normal conditions; therefore, a drug that inhibits expression of ARE-mRNAs should cause reduced side effects and (ii) several ARE-containing genes are involved in cancer progression such as proto-oncogenes, cytokines, growth factors, and invasion factors therefore, the targeting of abnormal ARE-function in cancer allows a specific yet collective normalization of the expression of a large group of genes by a single drug.

  A cell based screening platform is developed in the framework of this project that comprises a unique post-transcription-specific gene reporter expression system in addition to automation equipment. The drug screen involves 1280 FDA approved drugs representing the greatest possible degree of drug-likeness, chemical and pharmacological diversity and bioavailability and safety in humans.

- Post-transcriptional host response to intracellular bacterial pathogens – Highly recommended by American Association for the Advancement of Science (AAAS) review. SAR 1,721,800.00 was granted for this project.

  According to the World Health Organization (WHO) infectious and parasitic diseases remain the second leading cause of death in humans. Many intracellular bacterial pathogens produce cyclic di-AMP (c-di-AMP), a newly discovered bacterial second messenger that can induce host type I interferon response in human macrophages. In this project we are investigating the activity of the host cellular post-transcriptional regulation machinery in response to intracellular c-di-AMP. We have already discovered non-canonical c-di-AMP-dependent phosphorylation signaling pathways that lead to the activation MAP kinases resulting in altered host IFN and other cytokines mRNA decay level.

SELECTED ACHIEVEMENTS

- We have reported the first and the largest cytokine and chemokine screen (the human cytokinome, with >240 members) that involve in the modulation of type I and type II IFN responses in a cell line model. Certain cytokines appear to augment the IFN-β response through the NF-κB pathway. The novel IFN-like cytokines including

(Betacellulin, IL-11 and IL-17F) augmented the antiviral activity of IFN-α against several RNA viruses, including encephalomyocarditis virus, vesicular stomatitis virus, and influenza virus, in susceptible cell lines. Overall, the study represents a large-scale analysis of cytokines for enhancing the IFN response and identified the involvements of these cytokines on the enhancement of Stat1, IFN-induced gene expression, and antiviral activities.

- Issued U.S. Patent. US20090181427. HYBRID 3′ UNTRANSLATED REGIONS SUITABLE FOR EFFICIENT PROTEIN EXPRESSION IN MAMMALIAN CELLS. Filed: 2009. Issued: 2015

PUBLICATIONS

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- Mahmoud L, Al-Enezi F, Al-Saif M, Warsy A, Khabar KS*, Hitti EG. 2014. Sustained stabilization of Interleukin-8 mRNA in human macrophages. RNA Biology. 11(2):124-33.
- Al-Ahmadi, W., Al-Ghamdi, M., Al-Souhibani, N., and K.S.A Khabar 2013. "miR-29a inhibition normalizes HuR over-expression and aberrant AU-rich mRNA stability in invasive cancer". *The Journal of Pathology*, 230, 28-38.
- Saleh SM, Parhar RS, Al-Hejailan RS, Bakheet RH, Khaleel HS, Khalak HG, Halees AS, Zaidi MZ, Meyer BF, Yung GP, Seebach JD, Conca W, Khabar KS, Collison KS, Al-Mohanna FA. "Identification of the tetraspanin CD82 as a new barrier to xenotransplantation." *J Immunol*. 2013 Sep 1;191(5):2796-805.

DEPARTMENT OF MOLECULAR ONCOLOGY

DEPARTMENT OF MOLECULAR ONCOLOGY

ACTING CHAIRMAN

Abdelilah Aboussekhra, PhD

ADMINISTRATIVE SUPPORT STAFF

Robin Seamer

THE MOLECULAR ONCOLOGY DEPARTMENT IS A NEWLY ESTABLISHED department with the major goals to enhance the understanding of the molecular basis of cancer, to act as a catalyst for translational cancer research, and to promote the movement of that knowledge into the prevention and management of cancer. The department is composed of five sections: Breast Cancer; Cancer Biology & Experimental Therapeutics; Molecular Endocrinology; Translational Cancer Research and Cancer Epigenetics.

We have had a year of growth and development and there have been significant scientific achievements, including several publications, organization of seminars and workshops, active participation in various conferences and meetings, submission of grants, and training several students at different levels. In addition, public awareness has been a particular focus for Dr. Fahad Al-Khodairy and Dr. Suad Al-Abdullah. Moreover, Dr. Ali AlZahrani was very active in establishing the Research Center at KFSH&RC Jeddah.

BREAST CANCER RESEARCH

HEAD

Suad M. Bin Amer

STAFF

Amal Qattan, PhD *(Postdoctoral Fellow)*

Eman Barhoosh *(Grant – Research Technician)*

Shafeega Eltabache *(Grant – Research Technician)*

Editha Cabal *(Administrative support - Grant)*

BREAST CANCER IS A MAJOR CAUSE OF MORBIDITY AND MORTALITY among females in Saudi Arabia. Clinical observations indicate that the breast cancer developed before the age of 45 accounts for 45% of all female breast cancers in Saudi Arabia, as compared to 9.6% in USA. Breast cancer in young Saudi females is more aggressive in nature with poor prognosis and disease free survival. Thus, new diagnostics and prognostic and therapeutic markers are needed. It is also widely held that breast cancer initiates as the premalignant stage of atypical ductal hyperplasia (ADH), progresses into the pre-invasive stage of ductal carcinoma in situ (DCIS), and culminates in the potentially lethal stage of invasive ductal carcinoma (IDC). Genome-wide microarray-based gene expression analysis would be expected to provide a new opportunity to discover genes specifically activated or inactivated during the progress of a breast cancer. We expect to conduct a multidisciplinary research program aiming at understanding the causes of breast cancer in Saudi population and in turn to investigate novel therapeutic approaches. The aim of our unit is to establish molecular profiling of breast tumors to uncover the heterogeneity of this disease and to offer novel insights into tumorigenesis and therapy management.

RESEARCH PROJECTS

PROJECT TITLE: Determination of DNA Methylation Profile of Breast Cancer Patients to Develop Diagnostic and Prognostic Biomarkers

The grant for this project was approved by NSTIP (KACST)

PRINCIPAL INVESTIGATOR: *Dr. Suad Mohamed Bin Amer*

PROJECT DESCRIPTION: Breast cancer remains one of the most frequent cancers among women of every nationality. The late onset of symptoms and uncertain course of the disease contribute significantly to the mortality resulting from this cancer. Breast cancer is usually detected through the traditional triple test of physical examination, mammography and aspiration cytology. Although such tests have resulted in the early detection of cancer there is still a need to develop new strategies which could detect cancer in the preclinical and pre-symptomatic phase. In addition, these newer strategies should be able to detect and predict metastatic, recurrent and chemotherapy resistant disease. Several studies have shown that cancer patients have high serum levels of tumor specific DNA alterations, with over 90% of circulating DNA being derived from tumors. The most common epigenetic modification of the DNA in cancers is "DNA methylation". Modifications in methylomes are early events in cancers and remain involved throughout the process of oncogenesis. Investigators have previously shown that the aberrant modifications in the DNA methylation patterns can be used as robust biomarkers for diagnosing and prognosticating breast cancer. However, these aberrant changes in the DNA methylation patterns have been shown to be population specific. We aim to develop DNA methylation based biomarkers to 1) diagnose breast cancer 2) predict the metastatic potential and chemotherapy resistance in breast cancer patients from Saudi Arabia.

FUTURE RESEARCH DIRECTION

- We are in the process of examining in detail the gene expression signatures characteristic of the sequential stages (DCIS and IDC) of disease in our Saudi breast cancer patients, relating to the DNA methylation profile. We are seeking to identify a subset of genes with quantitative expression levels and DNA methylation profiles which correlate with an advanced tumor grade and also with the transition from DCIS to IDC respectively.
- We will also perform immunohistochemistry to validate the signature genes identified for a young group, a pre-menopause group and a post-menopause group of Saudi breast cancer patients

PROJECT TITLE: Micro-RNAs as Biomarkers for Diagnosing Breast Cancers

RAC # 2110016

PRINCIPAL INVESTIGATORS: *Dr. Suad Mohamed Bin Amer and Dr.Amal Qattan*

PROJECT DESCRIPTION: Breast Cancer remains one of the commonest cancers affecting women worldwide. To date several genetic, epigenetic, and proteinaceous biomarkers have been found to be associated with the disease, but their utility as robust indicators of disease remains uncertain. In light of this, there is a need to identify robust, specific as well as sensitive biomarkers which will be useful for detecting breast cancers and differentiate between aggressive and non-aggressive tumors. Micro-RNAs (miRs) are small 18-24 nucleotide RNAs which regulate the expression of approximately 30% of human genes. In cancers their expression is frequently dysregulated. Contributions from a number of laboratories have demonstrated that different cancers are associated with distinct miR profiles.

Recently, miRs have been found in significantly large copy numbers in the serum/plasma of cancer patients. The stability of the serum/plasma miRs is not compromised even if the samples are treated with RNase or incubated at room temperature over prolonged periods or subjected to repeated freeze-thaw cycles (1). Given that miRs are stable in serum/plasma, our goal is to identify a discrete set of miRs which are breast cancer-specific and which can therefore be employed as disease predicting biomarkers. To this end, we propose to carry out two following tasks: (1) Identify breast cancer-specific miRs by comparing the miR profiles derived from serum/plasma samples of breast cancer patients with those from healthy control individuals; (2) Evaluate the usefulness of identified miRs as reliable biomarkers for the early diagnosis and for progression of disease.

PUBLICATIONS

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- Al-Moghrabi N, Nofel A, Al-Yousef N, Madkhali S, Bin Amer SM, Alaiya A, Shinwari Z, Al-Tweigeri T, Karakas B, Tulbah A, Aboussekhra A. The molecular significance of methylated BRCA1 promoter in white blood cells of cancer-free females *BMC Cancer*. 2014 Nov 17;14:830. doi: 10.1186/1471-2407-14-830.
- Dilek Colak, Asmaa Nofal, AlBandary AlBakheet, Maimoona Nirmal, Hatim Jeprel, Abdelmoneim Eldali, Taher. Al-Tweigeri, Asmaa. Tulbah, Dahish. Ajarim, Osama. Almalik, Mehmet S. Inan, Namik kaya, Ben H. Park Suad M. Bin Amer. Age –Sepecific Gene Expression Signatures for Breast Tumors and Cross-Species Conserved Potential Cancer Progression Markers in Young Women, *PLoS one*, 2013 :Vol.8(5):1-13
- M. S. AlSalhi, S. Bin Amer, K. Farhat,D. Rabah, S. Devanesan,M. Atif, V. Masilamani, and Reem. K.. S. AL-Dakheel. Optical Biopsy of Breast Cancer Tissue. *Laser Methods in Chemistry, Biology, and Medicine* July 9,2012.
- Al-Jammaz,* B. Al-Otaibi, S. Okarvi, S. Bin Amer and J. Amarty. Synthesis and in vitro and in vivo evaluation of fluorine-18 labeled folates: Potential PET radiopharmaceuticals, *J. Nucl. Med. Biol.*, 2011.
- Al Jammaz, B. Al-Otaibi, S. Amer, N. Al-Hokbani and S. Okarvi, Novel Synthesis and Preclinical Evaluation of Folic Acid Derivatives Labeled with 18F[FDG] for PET imaging of Folate Receptor-Positive Tumors, *J. Nucl. Med. Biol.*, in press 2012. Available Online.
- AlJammaz, B. Al-Otaibi, S. Amer, J. Amartey and S. Okarvi, Preclinical evaluation of fluorine-18 labeled bombesin peptide analogs as potential PET radiopharmaceuticals for breast cancer imaging, IAEA proceeding, Accepted.

ABSTRACTS

- Al Jammaz, B. Al-Otaibi, S. Okarvi and S. Amer, Novel Synthesis and Preclinical Evaluation of Folic Acid Derivatives Labeled with 18F[FDG] for PET imaging of Folate Receptor-Positive Tumors, EANM, Birmingham, UK, October 2011
- AlJammaz, B. Al-Otaibi, S. Amer, J. Amartey and S. Okarvi, Preclinical evaluation of fluorine-18 labeled bombesin peptide analogs as potential PET radiopharmaceuticals for breast cancer imaging, IAEA IPET, Vienna, Austria, November 2011.
- AlJammaz, B. Al-Otaibi, S. Amer, N. AlHokbani and S. Okarvi, Synthesis and in vitro and in vivo evaluation of 67/68Ga-NOTA-folates for folate receptor-positive tumor imaging, fluorine-18 labeled bombesin peptide analogs as potential PET radiopharmaceuticals for breast cancer imaging, EANM Radiopharmacy, Nanets, France, April, 2012.

CANCER BIOLOGY AND EXPERIMENTAL THERAPEUTICS

HEAD

Abdelilah Aboussekhra, PhD

STAFF

Huda H. Al-Khalaf, PhD *(Adjunct Scientist, KACST)*

Maysoon M. Al-Ansary, PhD *(Adjunct Scientist, KSU)*

Syed Islam, PhD *(Associate Scientist)*

Siti-Faujiah Hendrayani, MSc *(Research Technician)*

CANCER IS A COMPLEX AND HETEROGENEOUS GENETIC DISEASE that results from the accumulation over age of a plethora of genetic and epigenetic alterations in various genes, which leads to uncontrolled cell proliferation and resistance to cell death. In addition, a higher order cell-cell interaction between cancer cells and their microenvironment is capital for tumor formation and spread. The major goals of this research section are to participate in understanding the fundamental processes of carcinogenesis, to elucidate the role of stromal cells in breast cancer onset and spread, and also the identification of novel natural molecules with potent anti-cancer effects. We are also interested in decorticating the role of obesity in breast development and spread. In addition, we assess the anti-carcinogenic effect of PAC (a curcumin analogue) and eugenol on various cancer cells both *in vitro* and *in vivo*. We are also aiming at targeting tumors through neutralizing the procarcinogenic effects of stromal cells using various approaches.

RESEARCH PROJECTS

PROJECT TITLE: Investigation of the Role of Stromal Fibroblasts in the Development of Breast Carcinoma: The Tumor Suppressor p16^{INK4A} Protein as Target

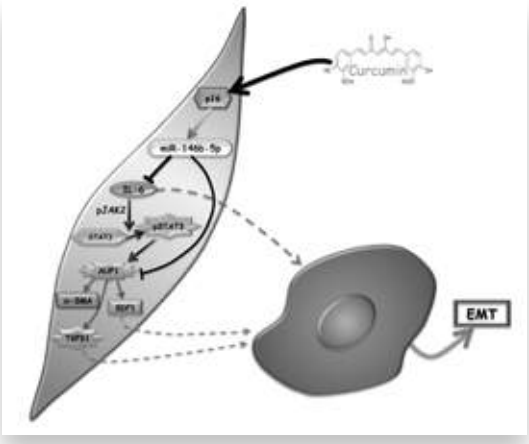
RAC # 2080009

National Science, Technology and Innovation Plan (NSTIP), Project Code: MED480-20

INVESTIGATORS: *A. Aboussekhra (PI), Mysoon Al-Ansary and Siti-Faujiah Hendrayani*

PROJECT DESCRIPTION: In the present proposal we are aiming at elucidating the functional interplay between stromal fibroblasts and breast carcinoma. More precisely we will study the role of the tumor suppressor p16 in the stromal-tumor interaction. To this end, we investigate p16 expression level in Carcinomas-Associated Fibroblasts (CAFs) and their corresponding Tumor Counterparts Fibroblasts (TCFs) from the same patient. Furthermore, we study the effect of p16 down-regulation, using p16 siRNA, on the molecular and cellular features of breast stromal fibroblast cells and on the proliferation of breast carcinomas. The resulting data will provide new insights into the importance of breast stromal fibroblasts in the development and treatment of carcinomas and the active involvement of p16 in this complex phenomenon.

PROGRESS: We have shown this year that the tumor suppressor p16^{INK4A} protein inhibits the pro-carcinogenic effects of breast stromal fibroblasts through repressing the expression/secretion of IL-6. Indeed, p16^{INK4A} suppresses IL-6 at the mRNA and protein levels. This effect is mediated trough miR-146b-5p, which inhibits IL-6 expression through a specific sequence at the IL-6 3'UTR. In addition, we present clear evidence that miR-146b-5p inhibition is sufficient to transactivate breast stromal fibroblasts, which promote epithelial-to-mesenchymal-transition in breast cancer cells in a paracrine manner. By contrast, ectopic expression of miR-146b-5p in active fibroblasts abrogated their pro-carcinogenic effects. The physiological importance of miR-146b-5p inhibition was revealed by showing that the levels of pre-miR-146b-5p as well as its mature form are reduced in cancer-associated fibroblasts as compared with their normal adjacent counterparts from cancer-free tissues isolated from the same patients. Interestingly, treatment of active breast stromal fibroblasts with curcumin increased the level of the p16^{INK4A} coding CDKN2A mRNA and miR-146b-5p and suppressed IL-6, which confirms the repressive effect of these two tumor suppressor molecules on IL-6, and shows the possible "normalization" of cancer-related active fibroblasts. These results show that miR-146b-5p has non-cell-autonomous tumor suppressor function through inhibition of IL-6, suggesting that targeting this microRNA in breast stromal fibroblasts could be of great therapeutic value (Figure 1).



PROJECT TITLE: Study of the Anti-Cancer Properties of PAC (A Novel Curcumin Analogue) *in Vitro* and *In Vivo*
RAC# 2080027

INVESTIGATORS: *A. Aboussekhra (PI), Ibrahim Al-Jammaz, Abeer Al-Qasem and Basem Al-Otaibi*

PROJECT DESCRIPTION: We are aiming at investigating the anti-cancer effects of PAC on various cancer cell lines, and investigating the toxicity and the pharmacokinetics of this agent *in vivo*. In addition, we would like to confirm the anti-cancer potential of PAC *in vivo* using tumor xenografts in mice. Our principal goal is to show that PAC could be of great value as anti-cancer agent, with less side effects.

PROGRESS: We have shown that PAC induces apoptosis, mainly via the internal mitochondrial route, and inhibits cell proliferation through delaying the cell cycle at G2/M phase. Interestingly, the pro-apoptotic effect was mediated through STAT3-dependent down-regulation of cyclin D1 and its downstream target survivin. Indeed, change in the expression level of cyclin D1 modulated the expression of survivin and the response of CRC cells to PAC. Furthermore, using the ChIP assay, we have shown PAC-dependent reduction in the binding of STAT3 to the cyclin D1 promoter *in vivo*. Additionally, PAC suppressed the epithelial-to-mesenchymal transmission process through down-regulating the mesenchymal markers (N-cadherin, vimentin and Twist1) and inhibiting the invasion/migration abilities of the CRC cells via repressing the pro-migration/invasion protein kinases AKT and ERK1/2. In addition, PAC inhibited tumor growth and repressed the JAK2/STAT3, AKT/mTOR and MEK/ERK pathways as well as their common downstream effectors cyclin D1 and survivin in humanized CRC xenografts. Collectively, these results indicate that PAC has potent anti-CRC effects, and therefore could constitute an effective alternative chemotherapeutic agent, which may consolidate the adjuvant treatment of colon cancer.

PROJECT TITLE: Study the Potential Role of IL-6 in the Cross-talk Between Breast Carcinomas and their Stromal Fibroblasts
RAC# 2120034
National Science, Technology and Innovation Plan (NSTIP), Project Code: 11-BIO2077-20.

INVESTIGATORS: *A. Aboussekhra (PI), Nisreen Al-Moghrabi and Siti-Faujiah Hendrayani*

PROJECT DESCRIPTION: In this project we investigate the paracrine effect of breast cancer cells on the expression of the stromal fibroblast p16 protein and the consequent effects on these fibroblasts. This will provide new insights into the role of IL-6-p16 route in the cross-talk between mammary carcinomas and their stromal fibroblasts and will delineate the molecular mechanisms that support this functional interplay, which could ultimately lead to the identification of important molecular targets for future therapeutic approaches.

PROGRESS: We have recently shown that IL-6-dependent activation of breast stromal fibroblasts is persistent even in absence of the activating agent.

PROJECT TITLE: Aging and Cancer: Role of p16/p53 and Stromal Fibroblasts
RAC# 2090027

INVESTIGATORS: *Huda Al-Khalaf and Abdelilah Aboussekhra (PI)*

PROJECT DESCRIPTION: In the present proposal we investigate the molecular interplay between the two major tumor suppressor proteins p16 and p53 and elucidate their role in regulating the expression of different age-related proteins and pathways. We also address the molecular mechanisms that

underlie the age-dependent apoptosis resistance in fibroblast cells. Furthermore, we will study the interaction between stromal fibroblast and epithelial cells during aging, and determine the autocrine and paracrine mechanisms that permit cancer development and progression. Our major aim is to identify important age-related stromal secreted factors and determine their effects on carcinogenesis and the oncogenic pathways in breast epithelial cells.

PROGRESS: We have recently shown that $p16^{INK4A}$ and p53 co-regulate a plethora of transcripts. Furthermore, both proteins form a heteromer whose level increases in aging human fibroblasts and various mouse organs. The p16/p53 heteromeric complex is formed only in the presence of DNA. We have also shown that $p16^{INK4A}$ enhances the binding efficiency of p53 to its cognate sequence presents in the *CDKN1A* promoter *in vitro*, and both proteins are present at the promoters of *CDKN1A* and *BAX in vivo*. Importantly, the fourth ankyrin repeat of $p16^{INK4A}$ and the C-terminal domain of p53 were necessary for the physical association between these 2 proteins. The physiologic importance of this association was revealed by the inability of cancer-associated $p16^{INK4A}$ mutants to interact with p53 and to transactivate the expression of its major targets *CDKN1A* and *BAX*. Together, these results show a novel role for $p16^{INK4A}$ in enhancing DNA binding and transcriptional functions of p53 via physical interaction.

PROJECT TITLE: Unraveling the Molecular Link Between Obesity and Breast Cancer: Role of Adipocytes and $P16^{INK4A}$

RAC # 2140017

National Science, Technology and Innovation Plan (NSTIP), Project Code: 11-BIO159-20

INVESTIGATORS: *Abdelilah Aboussekhra (PI), Huda H. Al-Khalaf, Asma Tulbah, Adher Alsayed, Mohamed Amir Murad, Abdelaziz Jarman, Falah Al-Mohanna*

PROJECT DESCRIPTION: The worldwide increase in obesity reached epidemic proportions including in Saudi Arabia, and has been recently recognized as a disease. Epidemiological studies have associated obesity with increased risk for various chronic diseases such as cancer. However, the molecular mechanisms that underlie obesity-related cancer predisposition and progression have not been delineated. Since obesity is characterized by hypertrophy of adipocytes, and disruption of the normal balance of adipose tissue secretory proteins, its plausible that these cells support the initiation and/or progression of cancer through paracrine effects. Thereby, in the present proposal we are aiming at investigating the role of mature adipocytes in breast carcinogenesis.

PROGRESS: p16 is downregulated and leptin is up-regulated in breast cancer-associated stromal adipocytes and obese normal adipocytes (Figure 2).

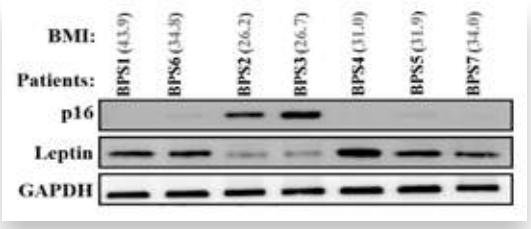


Figure 2. p16 is downregulated in normal adipocytes from obese women.

SELECTED ACHIEVEMENTS

1. $p16^{INK4A}$ and p53 co-regulate a plethora of transcripts and form a heteromer whose level increases in aging human fibroblasts and various mouse organs.

2. We have shown that the tumor suppressor p16 protein negatively regulates the expression/secretion of IL-6 through the activation of miR146b-5p, which represses the procarcinogenic effects of breast stromal fibroblasts.
3. PAC has potent anti-colon cancer effects through repressing the STAT3 AKT/mTOR and MEK/ERK oncogenic pathways.
4. p16 is downregulated and leptin is up-regulated in breast cancer-associated stromal adipocytes and obese normal adipocytes.

PUBLICATIONS

- Al-Ansari MM and Aboussekhra A. miR-146b-5p mediates p16-dependent repression of IL-6 and suppresses paracrine procarcinogenic effects of breast stromal fibroblasts. 2015 *Oncotarget*. Oct 6;6(30):30006-16.
- Abeer Al-Qasem, Huda A. Al-Howail, Mashael Al-Swailem, Amer Al-Mazrou, Basem Al-Otaibi, Ibrahim Al-Jammaz, Huda H. Al-Khalaf and Abdelilah Aboussekhra. PAC exhibits potent anti-colon cancer properties through targeting cyclin D1 and suppressing epithelial-to-mesenchymal transition. Mol. *Carcinogenesis*. 2015 Jan 16. doi: 10.1002/mc.22271. [Epub ahead of print].
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- Elkum N, Al-Tweigeri T, Ajarim D, Al-Zahrani A, Amer SM, Aboussekhra A. Obesity is a significant risk factor for breast cancer in Arab women. (2014) *BMC Cancer*. 29;14:788.
- Al-Ansari MM and Aboussekhra A. Caffeine Mediates Sustained Inactivation of Breast Cancer-Associated Myofibroblasts via Up-Regulation of Tumor Suppressor Genes. (2014) *PLoS One* 3;9(3):e90907. doi: 10.1371.
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- Al-Khalaf HH, Mohideen P, Nallar SC, Kalvakolanu DV, Aboussekhra A. The Cyclin-dependent Kinase Inhibitor $p16^{INK4A}$ Physically Interacts with Transcription Factor Sp1 and Cyclin-dependent Kinase 4 to Transactivate MicroRNA-141 and MicroRNA-146b-5p Spontaneously and in Response to Ultraviolet Light-induced DNA Damage. (2013) *J. Biol Chem*. 288(49):35511-25.
- Al-Ansari MM, Hendrayani SF, Shehata AI, Aboussekhra A. $p16^{(INK4A)}$ Represses the paracrine tumor-promoting effects of breast

stromal fibroblasts (2013). *Oncogene* 32 (18) 2356-2364.

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- Al-Khalaf HH, Aboussekhra A*. Survivin expression increases during aging and enhances the resistance of aged human fibroblasts to genotoxic stress. (2013) *AGE* 35(3):549-562.

CANCER EPIGENETIC SECTION

HEAD
Nisreen Al Moghrabi, PhD

STAFF
Nujoud Al-Yousef
Maram Al Showimi
Bushra Al-Shahrani

CANCER EPIGENETICS IS AN EXCITING AND EVOLVING AREA OF research that offers a valuable opportunity to identify cancer-specific changes, which can enable early detection and also be used in the clinic to improve diagnosis and prognosis of treated patients. Recent findings indicate epigenetic modifications as key factors in breast carcinogenesis. The main aims of this section are to determine the possible use of promoter methylation of different breast cancer-related genes in white blood cells as early detection biomarkers, in addition to the identification of potential correctors of these changes.

RAC APPROVED PROJECTS

PROJECT TITLE: *BRCA1* Epimutation and Breast Cancer Predisposition

Organization: King Abdulaziz City for Science and Technology (KACST)

The National Comprehensive Plan for Science and Technology

Riyals Awarded: 1,211,000

SUMMARY: Early onset breast cancer in Saudi Arabia is a serious problem. The proportion of breast cancer that develops before the age of 40 represents 26.4% of all female breast cancers compared to 6.5% in USA. In our previous study (published in 2011), we examined the frequency of breast cancer susceptibility 1 (*BRCA1*) methylation in 47 Saudi female patients, diagnosed with locally advanced breast carcinoma and we have found *BRCA1* promoter hypermethylated in 27.6% (13/47) of cases. Additionally, 30.7% of those hypermethylated cases were of the triple negative breast cancer subtype (4/13). Unexpectedly, methylated *BRCA1* promoter was also detected in 8 out of 73 samples (10.9%) of normal peripheral white blood cells (WBC). In this study, we are elaborating on these results by addressing two main questions: (I) what is the molecular significance of the presence of methylated *BRCA1* promoter in PBMC of healthy females, and is it an indicator of breast cancer predisposition? (II) What is the prevalence of *BRCA1* promoter methylation among early-onset triple-negative breast cancer patients? The resulting data will provide new insights into the functional significance of *BRCA1* methylation in young healthy females leading to its potential use as a molecular biomarker for detecting predisposed individuals at a far early age.

PROJECT TITLE: *BRCA1* Methylation in Newly Born Female Babies: The Molecular Significance and Transmission

Organization: King Abdulaziz City for Science and Technology (KACST).

The National Comprehensive Plan for Science and Technology:

Riyals Awarded, 1,364,250

SUMMARY: We have provided clear evidences that healthy women with *BRCA1* methylation in their WBC have, besides *BRCA1* methylation, modulation in the methylation and expression of other breast cancer-related genes, which may advocates the risk for developing breast cancer. Although the inheritance of some methylated cancer suppressor genes, MLH1 and MSH2, has been previously reported, *BRCA1* epimutation has not been documented to be a heritable change yet as no significant association has been found between *BRCA1* promoter methylation in WBC and a family history of breast cancer. Yet, in a recent pilot study, we have found that three newly born female babies, together with their mothers, have methylated *BRCA1* promoter in their WBC from cord and peripheral blood, respectively. This suggested the possible inheritance of this epigenetically modified gene. In the present study, we are aiming at addressing two main questions: (I) Does *BRCA1* promoter methylation occur as germline (with evidence of inheritance) or constitutional (no evidence of inheritance) epimutation. (II) What is the molecular significance of the presence of methylated *BRCA1* promoter in WBC of newly born female babies? The resulting data will help in understanding the functional significance of *BRCA1* methylation in newly born female babies and its possible inheritance leading to its potential use as a molecular biomarker for detecting predisposed individuals at the beginning of age.

PROJECT TITLE: Epigenetic Effect of Curcumin in Breast Cancer Cells

SUMMARY: Epigenetic alterations, which play an important role in the initiation and progression of cancer, are dynamic processes that are influenced by environmental, lifestyle and dietary factors.

DNA methylation, which plays an important role in regulating gene expression, is the most studied epigenetic modification. One of the important differences between genetic and epigenetic alteration is that the latter is a reversible process, which makes it a highly attractive clinical option for the prevention and treatment of cancer. Based upon this concept, epigenetic therapy is currently being explored, with the goal of preventing cancer cells from acquiring aberrant DNA methylation and helping to restore 'normal' DNA methylation and gene expression patterns to crucial cancer-related genes. Yet, the use of synthetic demethylating agents has adverse side effects due to the fact that they are narrow in their specificity. In this study we are exploring the epigenetic effect of curcumin, which is a natural compound derived from the spice turmeric, on several breast cancer cell lines representing different molecular subtypes of the disease. The resulting data will assist in the potential use of this natural product as a breast cancer preventive agent

PROJECT TITLE: Identification of the Mutational Spectrum and Frequencies of *BRCA1* and *BRCA2* genes in Saudi Breast and Ovarian Cancer Populations

Organization: King Abdulaziz City for Science and Technology (KACST)

The National Comprehensive Plan for Science and Technology

Riyals Awarded 1,999,000

SUMMARY: Familial breast and ovarian cancers are predicted to constitute 15–20% of these two women malignancies in the United States. Most hereditary breast and ovarian cancers are attributed to heterozygote germ line mutations in *BRCA1* and breast cancer susceptibility 2 (*BRCA2*) tumor suppressor genes. Both these genes are involved in DNA repair and genome integrity process in mammalian cells. Therefore the loss of function in either *BRCA1* or *BRCA2* due to inherent deleterious mutations and loss of heterozygosity (LOH) causes genetic instability and subsequently cancer in many epithelial cell types especially including the breast and ovaries. *BRCA1* and *BRCA2* have been sequenced in many breast and ovarian cancer populations throughout the world. The frequency and spectrum of germ line mutations of *BRCA1* and *BRCA2* in breast and ovarian cancer populations vary greatly depending on the geographic location, race and ethnicity studied. Thousands of germ line mutations spanning the large coding regions of BRCA genes have been identified along with some population specific recurrent founder mutations. Most of these deleterious mutations are known to be protein truncating and missense mutations. Both *BRCA1* and *BRCA2* mutations are highly penetrant; women born with germ line *BRCA1* or *BRCA2* mutations have total risk of developing breast cancer up to 85% of time and/or 50% ovarian cancer by age 70. In Saudi Arabia, breast cancer is the highest cancer type of all malignancies; one in four cancer cases are attributed to breast and ovarian malignancies in the Kingdom. Most breast and ovarian cancers are diagnosed as early onset, which could be due to germ line mutations in *BRCA1* and *BRCA2* genes. In this study, we are sequencing *BRCA1* and *BRCA2* genes in 300 early-onset breast and ovarian cancer patients to identify the frequency and the spectrum of mutations in these populations. We are also screening individuals from high risk breast and ovarian cancer families to identify the Saudi specific founder mutations. The identification of the most prevalent mutations in *BRCA1* and *BRCA2* in Saudi cancer populations will help the breast and ovarian cancer awareness for more screening, lifestyle changes and facilitate targeted therapies (i.e., PARP inhibitors) directed to *BRCA1*/*BRCA2* mutations that are currently in clinical trials.

PROJECT TITLE: The potential Role of Il-6 in the Cross-Talk Between Breast Carcinomas and their Stromal Fibroblasts

Organization: King Abdulaziz City for Science and Technology (KACST)
The National Comprehensive Plan for Science and Technology
Riyals Awarded 1,672,000

SUMMARY: Breast cancer has a major impact on the health of women worldwide including Saudi Arabia, where it is considered the most frequently diagnosed cancer (22% of all female cancers) and the leading cause of cancer deaths among women. Mammary tumors are highly complex, composed of various types of cells that cross-react and all participate in the development and spread of tumor cells. Fibroblasts are the predominant cells of the stromal breast carcinomas, yet the genetic alterations that occur in these cells and their functional contribution to tumor development, progression and therapy are not well understood. In the present study we are aiming at elucidating the functional interplay between breast carcinomas and their stromal fibroblasts, and delineate the role of IL-6 in this cross-talk. More precisely, we are investigating the paracrine effect of breast cancer cells on the expression of the stromal fibroblast p16 protein and the consequent effects on these fibroblasts. Furthermore, we are identifying the secreted molecules that play the role of mediator between cancer cells and stromal fibroblasts and we are giving a special attention to IL-6, as we have obtained some preliminary data suggesting the involvement of this cytokine in modulating the expression of p16 in a paracrine manner. Additionally, we are studying the effect of IL-6 on the molecular and cellular features of breast stromal fibroblast cells and on the effect of these cells on the growth, angiogenesis, invasion/migration as well as gene expression in breast carcinomas. We are also studying the molecular basis that underlies IL-6-dependent p16 down-regulation and its consequent effects on stromal fibroblasts. The resulting data will provide new insights into the role of IL-6-p16 route in the cross-talk between mammary carcinomas and their stromal fibroblasts and will delineate the molecular mechanisms that support this functional interplay, which could ultimately lead to the identification of important molecular targets for future therapeutic approaches.

PUBLICATIONS

- Nisreen Al-Moghrabi, Asmaa Nofel, Nujoud Al-Yousef, Safia Madkhali, Suad M. Bin Amer, Ayodele Alaiya, Zakia Shinwari,Taher Al-Tweigeri, Bedri Karaks, Asma Tulbah, Abdelilah Aboussekhra. The molecular significance of methylated *BRCA1* promoter in white blood cells of cancer-free females *BMC Cancer* (2014) 14:830 (Highly accessed).
- Nisreen Al-Moghrabi, Abeer J. S. Al-Qasem. Aboussekhra Abdelilah. Methylation-related mutations in the *BRCA1* promoter in peripheral blood cells from breast cancer-free female *International Journal of oncology* (2011) 39: 129-135.

MOLECULAR ENDOCRINOLOGY

HEAD

Ali S. Alzahrani, MD, FACP

STAFF

Mai Al-Mohanna, PhD *Scientist*

AK Murugan, PhD *Scientist*

Ebtesam Qasem, BSc *Research Technical Assistant (Grant Employee)*

Meshael AlSwailem *Master Student*

THE MOLECULAR ENDOCRINOLOGY SECTION FOCUSES ON TWO main domains. The first is translational research on endocrine neoplasms, exploring the role of certain oncogenes and tumor suppressor genes in the pathogenesis of endocrine cancer and studying genetic mechanisms of endocrine tumors. We are also interested in the clinical aspects of molecular findings in these tumors relating the phenotypes with genotypes. Our aim is to define the molecular basis of the clinical variations that these tumors show in their presentations, response to therapy and prognosis.

The second aspect of our work is to study genetic abnormalities in a number of genetic endocrine diseases such as hormone resistance syndromes, congenital hypothyroidism, disorders of sex developments, genetic endocrine hypertension and others.

RESEARCH PROJECTS

PROJECT TITLE: Mutational Profile of Differentiated Thyroid Cancer in Saudi Arabia
Funding: RAC Approved
RAC# 2120 015

INVESTIGATORS: *Ali S. Alzahrani, MD, Mai Al-Mohanna, PhD, Hindi Al-Hindi, MD, Mohammed Akhtar, MD, PhD, Yufei Shi, MD*

PROJECT DESCRIPTION: In this project, mutations in BRAF, RAS and many other genes known to be involved in thyroid cancer are being characterized. We study their correlation with histopathological features and outcomes of thyroid cancer.

PROGRESS: We have completed comprehensive mutation detection in several genes for about 300 cases of thyroid cancer. We presented 3 posters in the most important endocrine meeting, The Annual Endocrine Society Meeting. We published three important articles on this subject with novel findings in the Endocrine-related Cancer and Thyroid and Gene. We also written one review article on the role of TERT promoter mutations in thyroid cancer that has been provisionally accepted.

PROJECT TITLE: mTOR Mutations in Differentiated Thyroid Cancer; their Prevalence and Correlation with Histopathological Features and Outcome
Funding: RAC Approved
RAC # 2120 027

INVESTIGATORS: *Ali S. Alzahrani, MD, FRCPath, Hindi Al-Hindi, MD, Mai Al-Mohanna, PhD*

PROJECT DESCRIPTION: mTOR is a downstream mediator in the PI3K/AKT pathway. It interacts with multiple pathways and is widely involved in cellular growth and metabolism. Although frequently upregulated in many types of cancers, gene mutations have been only described at low frequencies in many tumors such as those of the gastrointestinal tract, breast and ovary. No previous study described mTOR mutations in DTC. We have screened a sample of thyroid cancer for mutations in the most frequently mutated exons in Mtor.

PROGRESS: We presented a poster in the 16th International Endocrinology Congress and 96th Endocrine Society Meeting, held in Chicago in June 2014. We also published an article on this in the journal Metagene. The Master student who performed this work was successfully awarded her degree as a result of this work.

PROJECT TITLE: Study of the Molecular Basis of Endocrine Genetic Disorders
Funding: RAC Approved
RAC# 2130 012

INVESTIGATORS: *Ali Alzahrani, MD, Afaf Alsagheir, MD, Mohammed Almehthel, MD, Bassam bin Abbas, MD, Mohammed Ahmed, MD, Abdulraof Almahfouz, MD*

PROJECT DESCRIPTION: Hereditary diseases are common in Saudi Arabia and hereditary endocrine diseases are not an exception. There are not many studies on the molecular basis of endocrine genetic diseases in Saudi Arabia. Most studies are occasional case reports or small number of families with genetic endocrine disorder. We are systematically studying genetic defects in several genetic endocrine disorders

PROGRESS: We have identified several known and novel mutations in many endocrine genetic disorders. A number of presentations in International Meetings were made. Two articles were published. Two were submitted and many more are in preparation. The work is still continuing in other disorders.

PROJECT TITLE: Genetic Defects in Matrix Metalloproteinases in Differentiated Thyroid Cancer
Funding: RAC Approved
RAC# 2120 013

INVESTIGATORS: *Ali Alzahrani, MD, Peter Hall, MD, Mohammed Akhtar, MD, Abdelilah Aboussekhra, PhD, Suad Alabdullah, PhD, Yufei Shi, MD*

PROJECT DESCRIPTION: Matrix Metalloproteinases (MMPs) are a large group of proteolytic enzymes that are involved in the degradation of the extracellular matrix. At least 23 members have been described in humans. They are synthesized in a variety of cells and secreted in the extracellular space although some of them remain associated with cell membranes. They have important roles in different physiological processes and are implicated in the pathogenesis of a number of conditions including cancer, atherosclerosis and arthritis. The role of the MMPs in tumor invasion and spread is believed to be related to their enzymatic degradation of the extracellular matrix. MMPs have been studied in different types of cancer. In differentiated thyroid cancer (DTC), MMPs expression has been studied but there has not been any systemic evaluation of possible genetic variations and their association with progression of DTC. We hypothesize that mutations and/or polymorphisms (SNP) in MMPs are associated with DTC tumorogenesis and progression. In this study, our objectives are to identify such genetic variants in MMPs, a frequently overexpressed MMP in thyroid cancer, and characterize the functional consequences of these mutations/SNPs if not previously described (novel mutations) and to study their clinicopathological correlation and prognostic value in a large sample of DTC.

PROGRESS: We have completed mutation detection phase in MMP2 and MMP8 in about 250 cases. A Master student who did the bench work has obtained her degree as a result of this work.

PROJECT TITLE: A Non-invasive and Sensitive "Molecular Blood Assay" to Evaluate Treatment Response/ Recurrence in Patients with Differentiated Thyroid Cancer
Funding: National Science, Technology and Innovation Plan (NSTIP) (Grant Program)
RAC #2130 034

INVESTIGATORS: *Ali Alzhrani, MD, Bedri Karkas, PhD, Mai Al Mohanna, Hindi Al Hindi*

PROJECT DESCRIPTION: In this project, we propose to test a recently developed highly sensitive molecular technique by following pre-identified somatic mutations in the plasma of patients treated for DTC in order to monitor the treatment response and tumor recurrence in these patients. We expect this assay to perform very well in these patients and that would lead to pioneering a very important tool for the follow up of patients with DTC. If validated, such an easily performed molecular marker would be of particular value in the follow up of patients in whom conventional methods are short of defining the status of the cancer, particularly in patients with elevated anti thyroglobulin antibodies, a situation that occurs in up to 25% of patients with DTC.

PROGRESS: This project is supported by KACST Biotechnology grant. We have completed the work on about 40 samples and found encouraging results. A poster was presented in the 97th Endocrine Society Meeting that took place in March 2015 in San Diego.

PROJECT TITLE: Molecular Basis of Disorders of Sex Development
Funding: National Science, Technology and Innovation Plan (NSTIP) (Grant Program)
RAC# 2130 018

INVESTIGATORS: *Ali Alzahrani, MD, Afaf Alsegheir, MD, Bassam Bin Abbas, Mai Al-Mohanaa, PhD, Yufei Shi, MD*

PROJECT DESCRIPTION: DSDs are not uncommon being reported in about 1:4500 births. Consanguinity is common and genetic diseases are equally common in Saudi Arabia. Although there is no formal assessment of the prevalence of DSD in Saudi Arabia, DSD are mostly hereditary in origin and it is our impression as practicing endocrinologists that these disorders are quite common. The genetic and molecular bases of DSD in Saudi Arabia have rarely been studied. Most of the published studies on DSD from Saudi Arabia are in the form of clinical and biochemical description of case series, single patients or families. In this proposal, we plan to systematically study the molecular basis of DSD in Saudi Arabia by studying a large sample of at least 200 non-selected cases of DSD.

PROGRESS: The work is ongoing on this project and one article was published and one submitted. Additional articles are being prepared as the work has been completed. Several families have been screened and known and novel mutations have been characterized. Some of this work was presented last year in the International Endocrine Congress and the Endocrine Society Meeting. Manuscripts are being prepared. This year, 4 more abstracts were submitted for the Endocrine Society Meeting to be held in Boston in 2016.

FUTURE RESEARCH DIRECTION

Our lab will continue to explore molecular mechanisms involved in endocrine malignancy correlating molecular findings with clinical and pathological features. Such translational research is the current trend in oncology in general and in endocrine oncology in particular. We are planning to fully characterize the mutational landscape of thyroid cancer in our patient population, an area that is hardly touched. We are also planning an *in vitro* and *in vivo* experimental work using some experimental drugs. We plan also to work on mechanisms of thyroid cancer mechanisms by *in vitro* manipulation of some oncogenes/tumor suppressor genes and assessing the effect of that on cell proliferation, invasiveness and the molecular pathways involved in thyroid cancer pathogenesis. Adrenal Cancer is another area that we got interested in recently and did some preliminary work in it and we are planning to explore it further. In addition, our lab is interested in characterizing the molecular basis of large number important genetic endocrine disorders that are quite common in our patient population.

PUBLICATIONS

- Al-Rasheed MM, Alzahrani AS, Macadam A, Overall A, Gard P, Dzimiri N. The potential role of the sodium iodide symporter gene polymorphism in the development of differentiated thyroid cancer. *Gene*. 2015;572: 163-168.
- Alzahrani AS, Alkhafaji D, Tuli M, Al-Hindi H, Sadiq BB. Comparison of differentiated thyroid cancer in children and adolescents (</ years) with young adults. Clin Endocrinol (Oxf). 2015.
- Murugan AK, Humudh EA, Qasem E, et al. Absence of somatic mutations of the mTOR gene in differentiated thyroid cancer. *Meta Gene*. 2015;6: 69-71.
- Murugan AK, Munirajan AK, Alzahrani AS. MicroRNAs: Modulators of the Ras Oncogenes in Oral Cancer. *J Cell Physiol*. 2015.
- Qasem E, Murugan AK, Al-Hindi H, et al. TERT promoter mutations in thyroid cancer: a report from a Middle Eastern population. *Endocr Relat Cancer*. 2015;22: 901-908.
- Xing M, Alzahrani AS, Carson KA, et al. Association Between BRAF V600E Mutation

and Recurrence of Papillary Thyroid Cancer. *J Clin Oncol*. 2015;33: 42-50.
- Zou M, Baitei EY, Al-Rijjal RA, et al. KRAS(G12D)-mediated oncogenic transformation of thyroid follicular cells requires long-term TSH stimulation and is regulated by SPRY1. *Lab Invest*. 2015;95: 1269-1277.
- Zou M, Baitei EY, Al-Rijjal RA, et al. TSH overcomes Braf-induced senescence to promote tumor progression via downregulation of p53 expression in papillary thyroid cancer. *Oncogene. 2015*.
- Alzahrani AS, Qasem E, Murugan AK, et al. Uncommon TERT Promoter Mutations in Pediatric Thyroid Cancer. *Thyroid*. 2016.

INTERNATIONAL PRESENTATIONS

97TH ENDOCRINE SOCIETY ANNUAL MEETING, SAN DIEGO, CA, MARCH, 2015

- Detection of $BRAF^{V600E}$ Mutation from Plasma DNA in Patients with Treated Papillary Thyroid Cance, Ali Saeed Alzahrani, MD, Riyadh, Saudi Arabia, Bedri Karakas, PhD, Molecular Oncology, King Faisal Specialist Hospital & research center, Riyadh, Saudi Arabia, Ebtesam Qasem, BSc, Department of Molecualr Oncology, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, Dania M Alkhafaji, MD, Department of Medicine, King Faisal Specialist Hospital & research center, Riyadh, Saudi Arabia, Hindi Al-Hindi, MD, Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital & research center, Riyadh, Saudi Arabia and Mai Almohanna, PhD, Department of Molecular Oncology, King Faisal Specialist Hospital & Research Centre.
- Low Frequency of $BRAF^{V600E}$ and TERT Promotor Mutations in Adrenocortical Tumors and Lack of Association of FGFR4 G388R Polymorphism with Adrenocortical Cancer Occurrence and Histopathological Score, Ali Saeed Alzahrani, MD, Riyadh, Saudi Arabia, Mai Almohanna, PhD, Department of Molecular Oncology, King Faisal Specialist Hospital & research center, Hindi Al-Hindi, MD, Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital & research center, Riyadh, Saudi Arabia, Ebtesam Qasem, BSc, Department of Molecualr Oncology, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia and Mohammed Almehthel, MBBS, ABIM, FRCP, Division of Endocrinology, University of British Columbia, Vancouver, BC, Canada
- Mutational Analysis of CYP11B1 in Patients with 11-ß Hydroxylase Deficiency. Meshael Alswailem, BSc[1], Doha Alhomaidah, MD[2], Ebtesam Qassem, BSc[3], Bassam Bin Abbas, MD[3], Afaf S Alsagheir[4] and Ali Saeed Alzahrani, MD[5], (1)Molecular Oncology, King Faisal Specialist Hospital & Research Centre, Riyadh, (2)Department of Pediatrics, King Faisal Specialist Hospital & Research Centre, (3)King Faisal Specialist Hospital & Research Centre, (4)king Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, (5)Riyadh, Saudi Arabia.
- Conginetal Lipoid Adrenal Hyperplasia Due to Star Mutations, Doha Alhomaidah, MD[1], Meshael Alswailem, BSc[2], Ebtesam Qassem, BSc[3], Afaf S Alsagheir[4], Bassam Bin Abbas, MD[3] and Ali Saeed Alzahrani, MD[5], (1)Department of Pediatrics, King Faisal Specialist Hospital & Research Centre, (2)Molecular Oncology, King Faisal Specialist Hospital & Research Centre, Riyadh, (3)King Faisal Specialist Hospital & Research Centre, (4)king Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, (5)Riyadh, Saudi Arabia.
- Congenital Adrenal Hyperplasia Secondary to 3-ß-Hydroxysteroid Dehydrogenase Type 2 Deficiency, Rahma Alasmari, MD, Ebtesam

Qassem, BSc[2], Meshael Alswailem, BSc[3], Bassam Bin Abbas, MD[2] and Ali Saeed Alzahrani, MD[4], (1)King Faisal Specialist Hospital & Research Centre, (2)Molecular Oncology, King Faisal Specialist Hospital & Research Centre, Riyadh, (3)Riyadh, Saudi Arabia.

- Primary Hyperparathyroidism As a Manifestation of Familial Paraganglioma Due to a Novel SDHB Mutation, Ali Saeed Alzahrani, MD, Riyadh, Saudi Arabia, Meshael Alswailem, BSc, Molecular Oncology, King Faisal Specialist Hospital & Research Centre, Riyadh and Ebtesam Qassem, BSc, King Faisal Specialist Hospital & Research Centre.
- Lung Metastases in Pediatric Differentiated Thyroid Cancer, Reem Almutairi, MD and Ali Saeed Alzahrani, MD, Riyadh, Saudi Arabia

GRANTS

- 12-BIO2952-20: A Non-invasive and Sensitive "Molecular Blood Assay" to Evaluate Treatment Response/Recurrence in Patients with Differentiated Thyroid Cancer
- 13-MED1154-20: Molecular Basis of Disorders of Sex Development in Saudi Arabia
- 10-BIO957-20: Molecular Characterization of the Mechanisms in BRAF Splicing Variants and Pseudogene Mediated Signaling and Thyroid Tumorigenesis in Transgenic Mice

OTHER ACHIEVEMENTS

- The 2015-2016 American Association of Clinician Endocrinologists (AACE) International Clinician Award, awarded to Dr. Ali Alzahrani and will be received offically during the 2016 AACE Annual Meeting to be held in Orlando, FL, May 2016.
- Editorial Board Member: Thyroid, the American Thyroid Association Journal.
- International Refree for the Endocrine Society Meeting Abstract Evaluation.
- Established a state-of the Art Research Center-KFSH&RC-Jeddah.
- President, AACE Gulf Chapter.
- A large number of national and international speaker invitations.
- Training a large number of Master students and rotating graduate and undergraduate.

TRANSLATIONAL CANCER RESEARCH SECTION

HEAD

Bedri Karakas, PhD

STAFF

Nada Al Kaff *(Research Technical Assistant)*

OUR SECTION IS FOCUSED ON BRIDGING THE GAP BETWEEN BASIC cancer research and clinical cancer care that is relevant to the local patient population.

We have been working to bring promising molecular diagnostic technologies to the clinical use. We are particularly interested in non-invasive methods to follow up cancer treatment response and early detection of relapses using blood circulating tumor DNA as a biomarker. We are also involved in identifying the mutational frequencies of important oncogenes and tumor suppressor genes in Saudi breast cancer population.

CURRENTLY ACTIVE FUNDED RESEARCH PROJECTS

PROJECT TITLE: Identification of the Mutational Spectrum and Frequencies of *BRCA1* and *BRCA2* Genes in Saudi Breast and Ovarian Cancer Populations
Source of Funding: KACST

OVERVIEW/AIMS: The main aim of this project is to identify the mutational frequency and location of breast cancer susceptibility (BRCA1/2) genes in Saudi breast and ovarian cancer patients. Another important aim is to find the penetrance of the mutations identified in family study for these two genes.

PROJECT TITLE: A Non-Invasive and Sensitive "Molecular Blood Assay" to Evaluate Treatment Response/ Relapse in Women with Breast Cancer
Source of Funding: KACST

OVERVIEW/AIMS: This project is focused on utilizing identifying somatic mutations in breast cancer tumors as biomarkers using a non-invasive assay for monitoring treatment response and detecting early relapses. This project's main aim is to bring a technology from bench to bedside for the use of local breast cancer population as an alternative or a complementary test to the imaging technologies.

PROJECT TITLE: A Non-invasive and Sensitive "Molecular Blood Assay" to Evaluate Treatment Response/ Recurrence in Patients with Differentiated Thyroid Cancer
Source of Funding: KACST

OVERVIEW/AIMS: This is a collaborative project with Molecular Endocrinology Section in our Department of Molecular Oncology. This project is also involved in non-invasive diagnosis of Thyroid cancers using pre-identified somatic mutations from the tumor. The identified mutations are later used to detect circulating tumor DNA in the blood of thyroid cancer patients during treatment. This project's results might be used in the clinical patient care in addition to other assays.

PROJECT TITLE: Cell Free Fetal DNA (cffDNA) in Maternal Circulation: An alternative Approach for Non-invasive Prenatal Diagnosis
Source of Funding: KACST

OVERVIEW/AIMS: This is as a collaborative project between our section and IVF section. This project focuses on detecting altered fetal DNA that circulates in the blood plasma of mother by bead-based emulsion PCR. All of the assays are being done in our Translational Cancer Research Section.

PROJECT TITLE: The Saudi Arabian Diseasome, A Network of Diseases: A Comprehensive Network-based Analysis Using Genomic, Transcriptomic and Proteomic Data Sets for Identification of Potential Markers for Diagnosis, Prognosis, and Therapeutic Outcome for Saudi Diseases
Source of Funding: KACST

OVERVIEW/AIMS: This is a collaborative project that is done by Dr. Dilek Colak in the Department of Biostatistics, Epidemiology and Scientific Computing. This project's aim is to analyze the already published data from Saudi patient populations try to generate some useful predictive, prognostic and surrogate biomarkers to be used during the treatment in the clinic.

SELECTED ACHIEVEMENTS

- Our section is involved in training and education of students.
- Involved in Journal Club Presentations.
- Scientific Presentations within Research Center and Hospital.

PUBLICATIONS

- Karakas B, Qubbaj W, Al-Hassan, Coskun S. Noninvasive Digital Detection of Fetal DNA in Plasma of 4-Week-Pregnant Women Following *In Vitro* Fertilization and Embryo Transfer. *PlosOne*, 2015; 10(5): e0126501.
- Al-Moghrabi, N., Nofel, A., Al-Yousef, N., Madkhali, S., Bin Amer, S. M., Alaiya, A., Shinwari Z., Al-Tweigeri T., Karakas B., Aboussekhra A. The molecular significance of methylated *BRCA1* promoter in white blood cells of cancer-free females. *BMC Cancer*, 2014; 14, 830. doi:10.1186/1471-2407-14-830.
- Karakas, B., Colak, D., Kaya, N., Ghebeh, H., Al-Qasem, A., Hendrayani, F., et al. (2013). Prevalence of PIK3CA mutations and the SNP rs17849079 in Arab breast cancer patients. *Cancer Biology and Therapy*, 2013; 14:10, 888–896.
- Garay, J. P., Karakas, B., Abukhdeir, A. M., Cosgrove, D. P., Gustin, J. P., Higgins, M. J., et al. The growth response to androgen receptor signaling in ERα-negative human breast cells is dependent on p21 and mediated by MAPK activation. *Breast Cancer Research*, 2012; 14(1), R27.
- Kaya, N., Colak, D., Albakheet, A., Al-Owain, M., Abu-Dheim, N., Al-Younes, B, Karakas, B et al. (2011). A novel X-linked disorder with developmental delay and autistic features. *Annals of Neurology*, 2012; 71:498–508.
- Konishi, H., Mohseni, M., Tamaki, A., Garay, J. P., Croessmann, S., Karnan, S., Karakas, B et al. Mutation of a single allele of the cancer susceptibility gene *BRCA1* leads to genomic instability in human breast epithelial cells. *Proceedings of the National Academy of Sciences*, 2011; 108(43), 17773–17778.

STEM CELL & TISSUE RE-ENGINEERING PROGRAM

STEM CELL & TISSUE RE-ENGINEERING PROGRAM

ACTING DIRECTOR

Ayodele A. Alaiya, MB.BS, Ph.D, FRCPath

SENIOR SCIENTISTS

Khaled Al-Hussein, PhD

Ayodele Alaiya, MB. BS, PhD, FRCPath

SCIENTISTS

Monther Al-Alwan, PhD

Ameera Gaafar Mohamed, PhD

Hazem Ghebeh, PhD

ADJUNCT/JOINT SCIENTISTS

Bandar Al-Saud, MD

Aida Al-Aqeel, MD, FRCP, FACMG

Zikra Al-Khayal, BDS, MS, FABPD

Mamdouh Al-Baqumi, MD, FASN, FACP

Walid Abbas M. Zaher MD, PhD

POST-DOCTORAL FELLOWS

Khaldoon Al-Romaih, PhD

Abdullah Al-Suliman, PhD *(on scholarship)*

RESEARCH ASSOCIATES

Manogaran Pulicat

Amer Al-Mazrou

RESEARCH ASSISTANTS

Zakia Shinwari

Rabab Al Alam

RESEARCH TECHNICIANS

Abdullah Al-Dhfyan

Eyad Al-Humaidan

Rayyanah Barnawi

Samiyah Alkaldi

Basma Alahideb

Maram Al Wahebi

Sheema Al Mozyan

ADMINISTRATIVE SUPPORT

April Grace T. Presto

LAB MANAGEMENT INFO. SYS. COOR.

Romeo L. Caracas

RESEARCH TECHNICAL ASSISTANT

Fatmah Abbas N. Mansour

GRADUATE STUDENTS

Amer Almaiman PhD

Program Titled: Proteomic Profile of Acute Myeloid Leukemia, Institute of Biosciences, Universiti Putra Malaysia *(Awarded PhD Degree, Dec 9, 2015)*

SECTIONS

- Stem Cell Banking and Tissue Engineering
- Stem Cell Biology
- Therapeutics and Biomarkers Discovery for Clinical Applications

OVERVIEW OF RESEARCH ACTIVITIES

The Stem Cell and Tissue Re-engineering Program, Research Centre, focuses on investigating the molecular and cellular mechanisms of stem cell biology, their application for therapeutic use in a number of clinical areas including, cancer, tissue transplant, and kidney-regeneration in addition to bone spinal cord injuries, cardiovascular, neurodegenerative, and autoimmune diseases. The department is working towards achieving the goal of excellence in stem cell research in the Middle East and worldwide. The program members are actively shifting their activities to conduct a range of translational and tissue re-engineering research in collaboration with KFSHRC laboratories and clinics, while continuing to pursue basic and pre-clinical research, and teaching. We are currently in dynamic collaboration with international institutions including but not limited to Harvard Medical School and its affiliated Hospitals, United States of America and Cancer Center, Karolinska University Hospital, Stockholm, Sweden. In addition to research and development, the program is committed to the training, recruitment and advancement of Saudi scientists, physicians, technicians and students.

SIGNIFICANT AND SCIENTIFIC ACHIEVEMENTS

- Fifteen (15) on-going RAC approved research projects.
- Three (3) in-house approved project for funding by KACST (project #s: 12-BIO2342-20, 13-BIO1486-20, 12-BIO2343-20) and 3 other collaborative KACST funded projects with other investigators within the RC
- Five (5) full scientific publications of research work were published in prestigious journals.(http://www.ncbi.nlm.nih.gov/pubmed/24914093, http://ndt.oxfordjournals.org/content/30/1/62.long, http://www.ncbi.nlm.nih.gov/pubmed/25500261, http://www.ncbi.nlm.nih.gov/pubmed/26245467, http://www.ncbi.nlm.nih.gov/pubmed/25697376).
- Six (6) Abstracts presented in international scientific conferences/meetings (USA, Greece, Canada, Sweden).
- Five (5) Abstracts presented in national scientific conferences/meetings.
- Supported young Saudi Arabian researchers, in pursuing training/higher education and postdoctoral fellowships at respected international institutes: Harvard Medical School, Harvard Hospitals (Dr. Khaldoun Al-Romaih-[completed May 2014]), and a PhD student at University Putra Malaysia (Dr Amer AlMaiman, Graduated Dec 9 2015). Established successful collaboration with national and international institutions on both research projects and education programs including, The Harvard Fellowships and Karolinska Hospital and Institutet, Stockholm, Sweden and Arabian Gulf University, Bahrain.
- Host "Summer Training Program" for gifted and future scientist students, Ibn Sina program, Princess Nora Girls University, and Alfaisal University

COLLABORATORS

INTERNATIONAL

- Harvard Medical School, USA.
- Brigham and Women's Hospital, Boston, MA, USA.
- Beth Israel Deaconess Medical Center

- University of Washington, WA, USA
- Cancer Center, Karolinska Hospital and Institute, Stockholm, Sweden
- Lund University, Lund, Sweden.
- Molecular Lab at Utrecht University, Netherlands to utilize high-resolution method for HLA typing.
- Northern Ireland Histocompatibility & Immunogenetics Laboratory, Belfast, Northern Ireland for allele frequencies.
- Pittsburgh Development Center
- Leiden University Medical Center, Dept. Immunohematology and Blood Transfusion, Eurotransplant Reference Laboratory, Leiden, the Netherlands.
- Finsen Laboratory, BRIC and DANSTEM, Copenhagen, Denmark.

NATIONAL

- Department of Pathology & Laboratory Medicine, KFSH&RC, Riyadh, KSA (Tissue and Stem Cell Banking for Solid Tumors, and Identification and Therapeutic Targeting of Cancer Stem Cells).
- Department of Pediatric Urology, KFSH&RC, Riyadh, KSA (Discovering Biomarkers for Urinary Tract Infection (UTI)).
- Department of Medicine, KFSH&RC, Riyadh, KSA (Discovering Markers for Classification of Lupus Nephritis and other kidney diseases)
- Renal Transplant Program, KFSH&RC, Riyadh, KSA (Discovering Markers for Organ Transplant/ Rejection).
- Cord Blood Bank, Department of Pathology and Laboratory Medicine, KFSH&RC, Riyadh, KSA.
- Department of Pediatrics, KFSH&RC, Riyadh, KSA (Discovering Markers for Polycystic Kidney Disease).
- Department of Neurosciences, KFSH&RC, Riyadh, KSA (Developing Markers for Epilepsy and Brain Tumors).
- Oncology Centre, KFSH&RC, Riyadh, KSA (Discovering Treatment Response Markers for Cancer Patients).
- Department of Surgery, KFSH&RC, Riyadh, KSA (Developing Stem Cell Banking and Discovering Markers for Breast, Colorectal, and Cancers and other Solid Tumors).
- Prince Fahad bin Salman Charity Association for Renal Failure Patients Care, Riyadh, KSA.
- Failure Patients Care, Riyadh (Initiated Kidney Health Research).
- Prince Salman Centre for Disability & Research, Riyadh, KSA.
- King Saud University, Riyadh, KSA (Research on Neurodegenerative Disease).
- Prince Fahad bin Salman Charity Association for Renal Failure Patients Care, Riyadh, KSA (Initiated Kidney Health Research).
- Several Research Units in the Research Center, KRSH&RC

RAC APPROVED RESEARCH ACTIVITIES

PROJECT TITLE: The Role of the Immunomodulatory Molecule B7-H1 (PD-L1) in the Initiation and Maintenance of Cancer Stem Cells
RAC# 2140 001

PRINCIPAL INVESTIGATOR: *Dr. Hazem Ghebeh*
CO-INVESTIGATORS: *Dr. Abdullah Alsuliman, Dr. Monther Al-Alwan, Dr. Taher Al-Tweigeri, Dr. Asma Tulbah*

PROJECT DESCRIPTION: In cancer, a small subset of the tumor cells acquires some of the stem cell features and thus named as "cancer stem cell" (CSC). There is mounting evidence that a hierarchy exists, where CSCs differentiate into cancer non-stem cells and form the bulk of the tumor. CSCs possess similar features to normal stem cells in their ability of inducing immune modulation. Unfortunately, possession of these features by CSCs contributes to their escape from

the immune system recognition and thus failure of the treatment and tumor relapse. How cancer stem cells in breast cancer specifically escape the immune system is not well known. In this project we have shown that PD-L1 is associated with cancer stem cells in breast cancer.

Using the publicly available dataset (TCGA) we found a high correlation between stemness of breast cancer cells and PD-L1 mRNA expression (Figure 1).

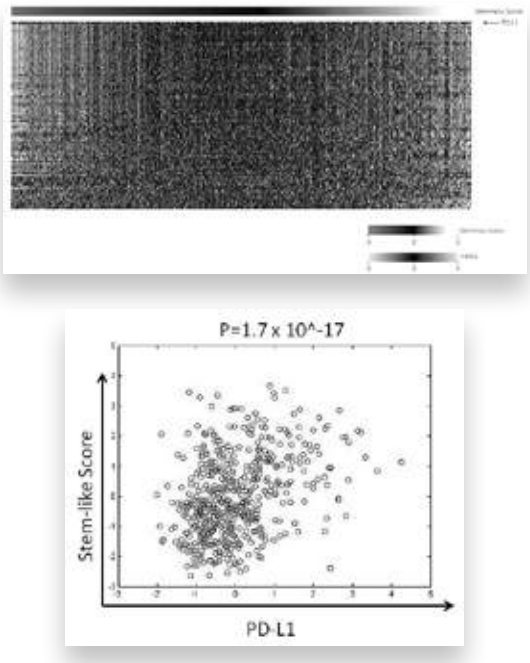


Figure 1. Correlation of PD-L1 expression and stemness of breast cancer using TCGA gene expression dataset. (Top) Heat map showing mRNA expression level stemness related genes and compared with PD-L1 expression as indicated with the arrow at the top. The samples in the data are arranged according to their stemness score. Bottom) Scatter plot of PD-L1 mRNA expression level in correlation with stemness score in TCGA breast cancer samples

In addition we demonstrated the critical role of PD-L1 in CSCs using Extreme Limiting Dilution Assay (ELDA) which showed that downregulating PD-L1 only resulting in the decrease in the frequency if PD-L1 from 1 in 315 cells to 1 in 1500 cells. (Table 1).

Table 1. Frequency of CSCs upon PD-L1 manipulation using ELDA

	Cells Seeded	1000	100	10	CSCs frequency
1	Sh-Cont	*4/6	5/6	2/6	1 in 316 cells
2	Sh-PD-L1	1/6	2/6	1/6	1 in 1500 cells

*The number of mice forming tumor over the total number of mice injected.

PROJECT TITLE: Proteomic Analysis of Human Breast Cancer Stem/Progenitor Cells
RAC # 2080 021, (Proteomics)

PRINCIPAL INVESTIGATOR: *Dr. Ayodele Alaiya*
CO-INVESTIGATORS: *Dr. Fouad Al-Dayel, Dr. Hind Al-Humaidan, Dr. Dilek Colak, Dr. Ghebeh Hazem, Dr. Asma Tulba, Dr. Taher Al-Tweigeri*

BACKGROUND: Many panels of surface markers including $CD44^{high}/CD24^{low}$, aldehyde dehydrogenase ($ALDH^{high}$), and differentiation markers like MUC-1 are currently being used independently or in combination to characterize cells with stem-like features. However, there is lack of universal utility of these markers with different breast cancer subtypes and their relationship to the normal mammary gland cells. This study aims to identify novel protein biomarkers specific to normal and malignant breast stem cells by comparing the protein fingerprints of stem/progenitor cells from normal and breast cancer tissues as well as different subtypes of breast cancer cell lines for their expressions of stem cell phenotypic protein profiles.

STUDY PHASES: We have divided the study into three phases using label free-quantitative Expression Proteomics platform on Waters Synapt G2 LC/MS/MS to analyze stem/ progenitor-like cells vs differentiated-like in:

1. Breast cancer cell lines
2. Normal tissue from donors
3. Breast cancer patients

AIMS: Analyze the proteome of Stem-like cells vs Differentiated-like cells in breast cancer cell lines as model of the different subtypes of breast cancer:

1. MCF-7 for Luminal-like
2. SK-BR-3 as representative of Her2/neu
3. MDA-MB-468 as representative of Basal-like
4. MDA-MB-231 as representative of Claudin-low

FLOW CYTOMETRY CELL SORTING STRATEGY

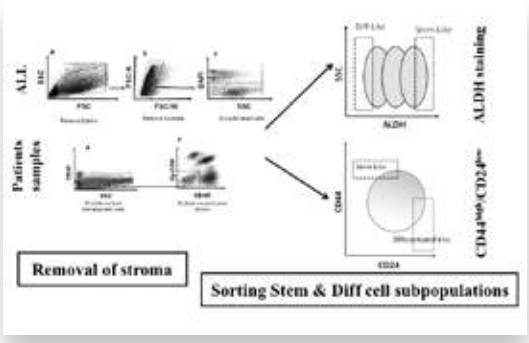


Figure 2. Cells from normal human breast tissues, human breast tumors, and cells from different subtypes of breast cancer cell lines (Table below) were Flow Cytometry-sorted using combinations of surface markers. The phenotypic characteristics of these cell populations were subsequently evaluated by Waters Synapt G2- label-free quantitative Nano-LC-MS-MS expression analysis

RESULTS:

- Protein expression profiles in different subtypes of breast cancer cell lines (SK-BR-3, MDA-MB-468 & MCF-7
- Each of the breast cancer cells were sorted into three subpopulations including: unsorted, stem cell positive and negative fractions.
- Only samples which showed increase in protein abundance in unsorted/positive compared to negative were chosen
- Among the above only proteins with more than 2 folds increase in the $ALDH^{high}$ or $CD44^{high}/CD24^{low}$ compared to unsorted cells were chosen
- P value < 0.005 & ≥ 2-Fold changes

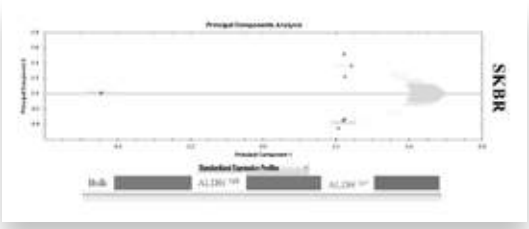


Figure 3. Principal Component Analysis of 299 differentially expressed proteins between sub populations of SKBR-3 breast cancer cells. Samples were separated into three distinct clusters of $ALDH^{high}$, $ALDH^{low}$ and unsorted bulk.

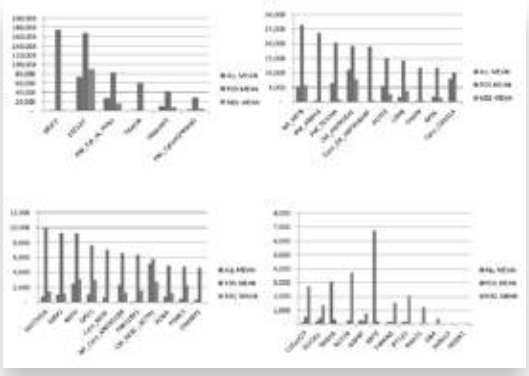


Figure 4. A quantitative comparison of some of the identified proteins expression between un-sorted, (Blue), stem cell-positive, (Red) and stem cell negative (green) cell populations from breast cancer SKBR-3 cells. Similar expression changes were observed in MDA-231 and MCF-7 breast cancer cell lines. The plot was generated using he expression dataset of some of the differentially expressed proteins. The localization/Stem Cell implications of some of the proteins are as indicated: Cyto=Cytosol/Cytoplasm, ER=Endoplasmic Reticulum, PM=Plasma Membrane, ESC=Embryonic Stem Cell, CM=Cell Membrane, Prol_Cell= Proliferating Cells.

Table 2: Partial list of some identified differentially expressed proteins across three subtypes of breast cancer SKBR-3 cells. A review of some of these molecules showed that they are implicated as stem/progenitor-like (*) and some as membrane proteins (**), thus indicating their potential usefulness as panel of objective stem cell markers.

Description	Gene Name	Stem Cells*	Membrane**
Rabenosyn-5 OS=Homosapiens	ZFYVF20		M
Fructose 1, 6-bisphosphate 1	FBP1	CSC-like	
Isoform 2 of RuvB-like 2	RUVBL2	ESC	
ATP-dependent DNA helicase Q1	RECQL	NSC	M
Keratin, type II cytoskelletal 8	KRT 8	mESC	
Signal recognition particle 9 kDa protein	SRP9		M
Isoform 2 of ATP binding cassette sub-family A member 5	ABCA5		M
Fibroblast growth factor receptor 1(Fragment) 4	FGFR1	hMSCs	M
Dolichyl-diphospooligosaccharide - protein glycosyltransferase subunit STT3A	STT3A		M
Kelch-like protein 7 (Fragment)	KLHL7		M
Isoform 3 of MAP/microtubule affinity-regulating kinase 3 OS=Homo sapiens	MARK3		M
Transferrin receptor protein 1 OS=Homo sapiens	TFRC		M
L-lactate dehydrogenase B chain OS=Homo sapiens	LDHB		M

SUMMARY

- We have identified new proteins that might be specific markers for identification of normal human mammary stem cells. Some of them have been implicated as potential stem cell markers
- The majority of the so far identified marker proteins are cell surface that can be used for sorting of alive cells and further functional analysis

FUTURE DIRECTIONS

- Confirm the differentially expressed protein markers by IHC or other methods
- Validate our findings by sorting of alive breast cancer cell types and subject them to biological/functional assays
- Validate the identified proteins by sorting of alive cells labeled with each of the newly identified markers alone or in combination and subject to biological/functional assays.

This data were presented at 14th Human Proteome Organization World Congress (HUPO 2015), September 27 – 30, 2015 Vancouver, British Columbia, Canada

PROJECT TITLE: Proteomics Approach to Biomarker Discovery in Aplastic Anemia
RAC #2060 021 (Proteomics)

PRINCIPAL INVESTIGATORS: *Dr. Ayodele Abdulkareem Alaiya, Dr. Mahmoud Al-Jurf*
CO-PRINCIPAL INVESTIGATORS: *Dr. Naeem Chaudhri, Dr. Hazzaa Al Zahrani*
CO-INVESTIGATORS: *Dr. Mai Al-Mohanna, Dr. Entezam Sahovic, Dr. Fahad Al Mohareb, Dr. Fahad AL Sharif, Dr. Hamad Al Omar, Dr. Ali Al Shanqeeti, Dr. Majed Dasouki, Dr. Syed Osman Ahmed*

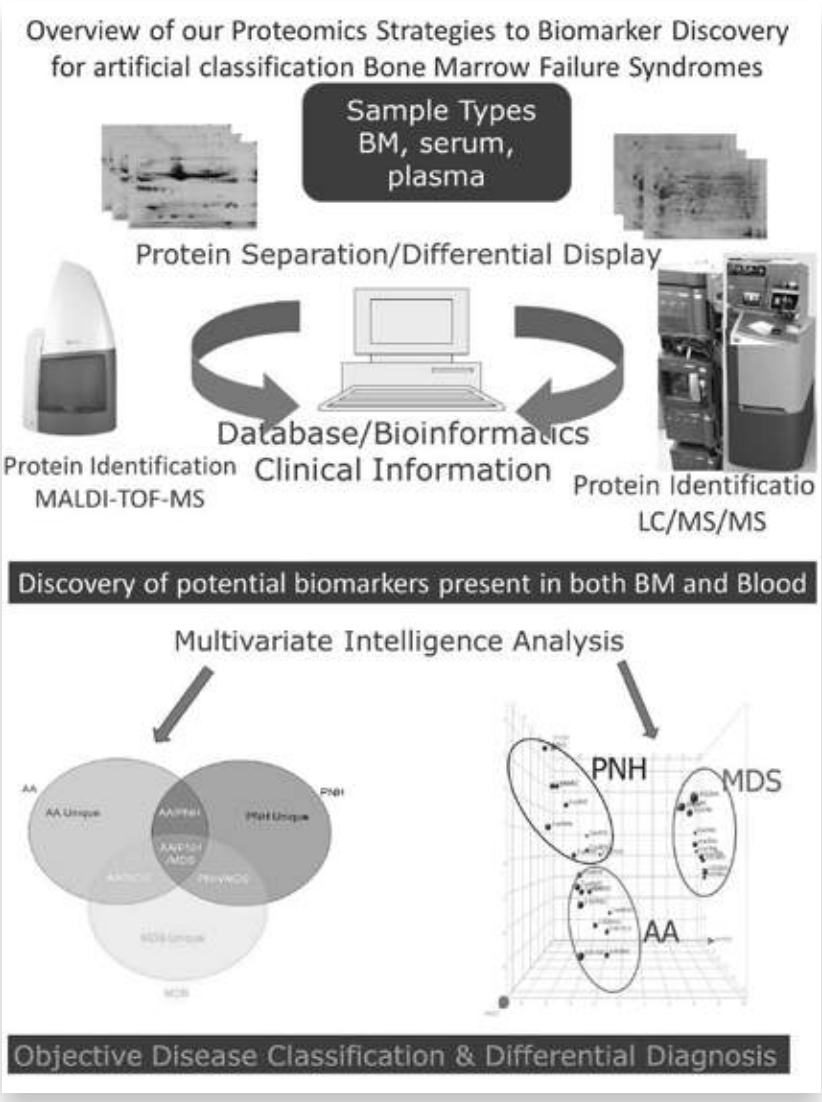
PROJECT DESCRIPTION: Bone marrow failure syndrome is an example of disease entity where accurate diagnosis of Severe Aplastic Anemia (SAA), Paroxysmal Nocturnal Hemoglobinuria (PNH) and Hypoplastic Myelodysplastic Syndrome (MDS) is very challenging. The aim of this study was to identify panels of disease–specific /disease-

associated proteins biomarkers to be used for more objective diagnosis and better prediction of disease prognosis of patients presenting with features of bone marrow failure syndromes.

EXPERIMENTAL DESIGN

Bone marrow plasma (MBP) and peripheral blood plasma (PBP) samples from 20 patients with bone marrow hypoplasia; including SAA/MDS/PNH were subjected to expression proteome analysis using label-free quantitative liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS).

Overview of the experimental strategies is as illustrated in the figure below.



RESULTS

LC/MS/MS PROTEIN IDENTIFICATION

- Approximately 300 unique protein species were identified of which 177 and 172 were significantly differentially expressed (> 1.5-∞- fold change & $p < 0.05$) in BMP and PBP respectively.
- These protein fingerprints independently discriminates patients into three distinct clusters; AA/MDS/PNH using unsupervised principal component analysis (Figure 7).
- Majority of the proteins were common to all, with 7 unique proteins in SAA, and only 1 unique protein in PNH (Figure 6A).
- Approx. 25% of the differentially expressed proteins were common between the two datasets from BMP and PBP. (Figure 6B).

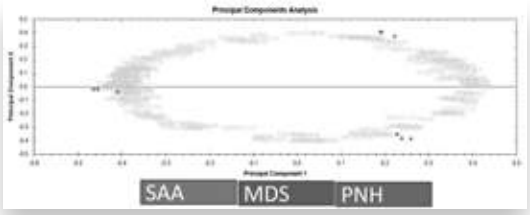


Figure 5: (A) Principal Component Analysis using dataset of 177 differentially expressed BMP proteins separated the samples into three main groups of PNH (5 cases, pooled into n=3) (Orange), MDS (5 cases, pooled into n =3) (Purple) and cluster of SAA(10 cases but pooled into n= 3 samples) (Blue). Some the identified proteins were implicated in hematological diseases as potential biomarkers using Ingenuity Pathway Analysis and their expression levels are indicated in Figure 4.

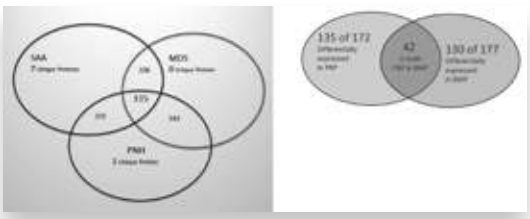


Figure 6: (A) Distribution of the total identified proteins from BMP between SAA, MDS & PNH and **(B)** Overlap of differentially expressed proteins between the two bodily compartments BMP and PBP.

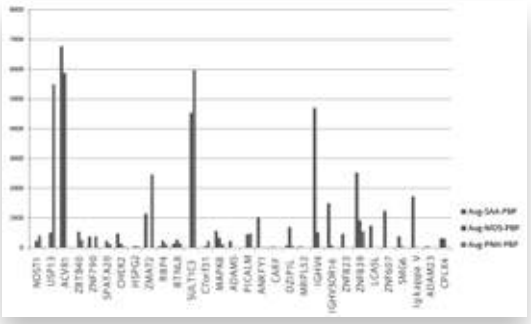


Figure 7: Expression profiles of some of the identified proteins that were differentially expressed between SAA, MDS, and PNH samples. The proteins were identified by tandem mass spectrometry using Synapt G2 HDMS™ (Waters).

- We demonstrated that quantitative proteome data can potentially be useful in discovery of novel disease-related/disease-specific biomarkers for differential diagnosis of BM failure syndromes.
- This data opens the possibility that validated studies can lead to the identification of clinically useful biomarkers protein signatures capable of as molecular diagnosis of BM failure entities.

CONCLUSION

- We demonstrated that quantitative proteome data can potentially be useful in discovery of novel disease-related/disease-specific biomarkers for differential diagnosis of BM failure syndromes.
- This data opens the possibility that validated studies can lead to the identification of clinically useful biomarkers protein signatures capable of as molecular diagnosis of BM failure entities.

GENETICS ANALYSIS

- Whole Exome Sequencing (WES): 98 gDNA samples had been processed so far.

- Telomere length assay: we setup a protocol using Roche's Light Cycler 480II which is undergoing optimization.
- Copy Number Variant (CNV) analysis using Oncosca-SNP arrays:
- CNV analysis was carried out in 26 gDNA samples.
- Genome wide Axiom arrays based SNP genotyping:
- SNP genotyping of 108 samples was done which identified multiple runs of homozygosity.

FUTURE RESEARCH DIRECTIONS

- To validate our findings especially the unique proteins in SAA and PNH
- To identify a panel genes among the overlap of the 42 proteins in both BMP and PBP, thus avoiding the risk of invasive procedure with ease of access to peripheral blood than BM aspiration.
- To validate in a larger sample cohorts; whether all the observed protein patterns would accurately predict the samples based on their clinical & biological characteristics.
- Analyze the completed NGS based data in order to identify pathogenic or likely pathogenic variants
  - Analyze the copy number (CNV) & SNP data & to test the remaining genomic DNA samples for SNP genotyping & CNV content.
  - Extract the HLA genotyping data on the patients with aplastic anemia and examine risk alleles/haplotypes for the development of aplastic anemia and complications related to therapy

PUBLICATIONS

- Alaiya et al; Biomarker for Accurate Diagnosis of Severe Aplastic Anemia, Hypoplastic Myelodysplastic Syndrome and Paroxysmal Nocturnal Hemoglobinuria PatientsThe American Society of Hematology (ASH) 57th ASH Annual Meeting in Orlando Florida, December 5-8, 2015 (Official website: (http://www.hematology.org/Annual-Meeting/) Abstract 2414I, December 3, 2015; Blood: 126 (23), (https://ash.confex.com/ash/2015/webprogram/Paper80511.html).

1. Saudi Mendeliome Group (89 co-authors). Comprehensive gene panels provide advantages over clinical exome sequencing for Mendelian diseases. *Genome Biol*. 2015 Jun 26;16:134. PMID: 26112015.]
2. Majed Dasouki, Syed Osman Ahmed, Ali Alahmari, Amal Jabr, Moheeb Ali Alawwami, Naeem A. Chaudhri, AlMohareb Fahad, Said Y Mohamed, Walid Rasheed, Hazza A Alzahrani, Mahmoud Aljurf. Improved Molecular Diagnosis of Aplastic Anemia/ Bone Marrow Failure Syndromes Using a Novel Comprehensive Next Generation Sequencing Gene Panel. *ASH/American Society of Hematology*. eblood. 2015.

PROJECT TITLE: Chronic Myeloid Leukemia: Development and Validation of Therapeutic Hematoproteomic Biomarkers, (Proteomics)
RAC# 2050 040

PRINCIPAL INVESTIGATOR: *Dr. Ayodele Abdulkareem Alaiya*
CO-PRINCIPAL INVESTIGATORS: *Dr. Mahmoud Al-Jurf, Dr. Naeem Chaudhri*
CO-INVESTIGATORS: *Dr. Mai Al-Mohanna, Dr. Entezam Sahovic, Dr. Fahad Al Mohareb, Dr. Fahad Al Sharif, Dr. Hamad Al Omar, Dr. Hazzaa Al Zahrani, Dr. Ali Al Shanqeeti*

PROJECT DESCRIPTION

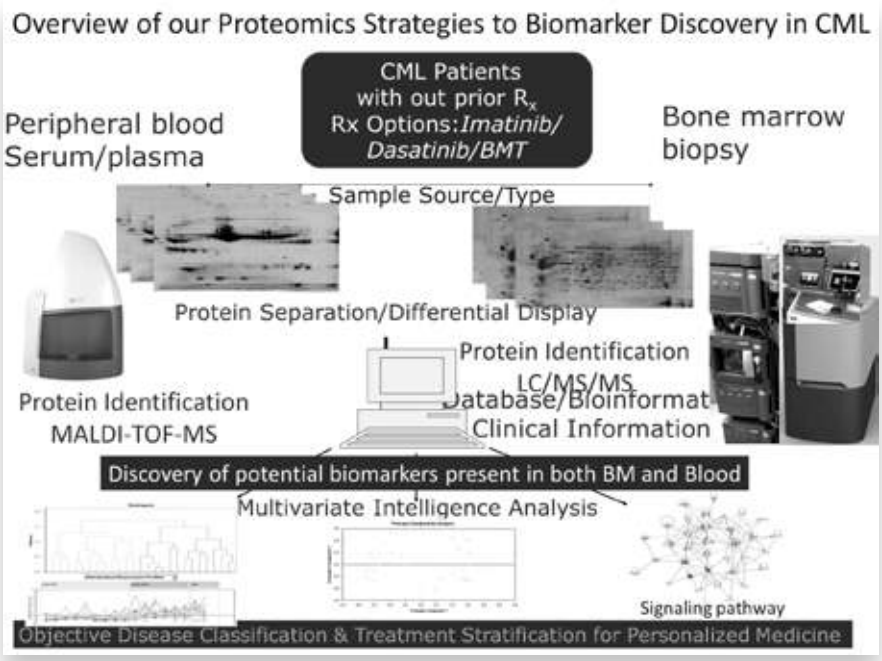
BACKGROUND: There is unmet need for objective selection of therapeutic agents and accurate prediction of response for Chronic Myeloid Leukemia (CML) patients. This study aim to

identify disease-specific/disease-associated protein biomarkers detectable in bone marrow and peripheral blood thus, requiring less invasive procedures for objective prediction of individual's best treatment options and prognostic monitoring of CML patients.

METHODS: Bone Marrow Plasma (BMP) and Peripheral Blood Plasma (PBP) samples from newly-diagnosed chronic–phase CML patients were subjected to expression-proteomics using combined quantitative-two-dimensional gel-electrophoresis (2-DE) and label-free liquid chromatography tandem mass-spectrometry (LC-MS/MS).

RESULTS: Unsupervised principal component analysis of 2-DE protein fingerprints at presentation and prior to therapy commencement accurately predicts 13 individuals that achieved Major Molecular Response (MMR) at 6 months from 12 subjects without MMR (No-MMR). The results were independently validated using LC-MS/MS analysis of BMP and PBP samples from patients that have more than 24 months followed up. One-hundred-sixty four (164) and 138 differentially- expressed (> 2-fold-change/$p < 0.05$) proteins were identified from PBP and BMP, respectively with only 57 proteins overlaps between the two datasets. The protein panels also discriminates accurately patients that stay on Imatinib treatment from patients ultimately needing alternative treatment.

CONCLUSIONS: We have identified protein signatures capable of objective prediction of molecular response and choice of therapy for CML patients at 6 months and beyond. Our expression-proteomics strategy is very promising for discovery of clinically useful biomarkers. These proteins might be valuable once validated, for: prediction of disease progression, treatment response and clinical outcome of CML patients as "personalized-medicine model".



RESULTS

PROTEIN FINGERPRINTING FOR PREDICTION OF TREATMENT OPTIONS FOR INDIVIDUALIZED THERAPY. A panel of 164 and 138 differentially expressed protein datasets derived from peripheral blood plasma (PBP) and bone marrow (BM) respectively, discriminates patients that stay on IM after 1 year of treatment from patients that ultimately required alternative treatment options (Second generation TKI/ others) (Figure 4). We have had more than 2 years follow up of these patients and the same dataset of potential protein biomarkers could still accurately separate all analyzed sample groups into their respective molecular response and treatment sub groups, indicating their usefulness for treatment monitoring as well as prediction of best choice of therapy for individual patient. Some of the identified proteins were implicated in hematological diseases as potential biomarkers using Ingenuity Pathway Analysis.

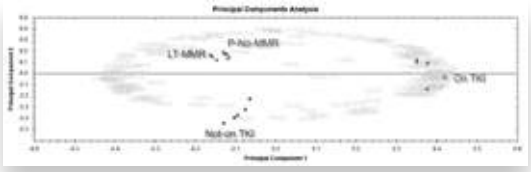


Figure 8: Unsupervised principal component analysis (PCA) plot of CML peripheral blood samples using the expression dataset of 164 identified proteins that were significantly differentially expressed (> 2- ∞- folds change, $p < 0.05$) between LT-MMR and P-No-MMR sample groups. The expression profiles of these proteins correctly predict patients with Major Molecular Response (LT-MMR, Blue) vs. No-Major Molecular Response (P-NoMMR, purple) as well as separate patients that stay on TKI after 1year of Imatinib Rx from patients ultimately requiring alternative treatment. Some of the identified proteins were implicated in hematological diseases as potential biomarkers using Ingenuity Pathway Analysis.

IDENTIFICATION OF PROTEINS CHANGES IN BM AS A REFLECTION OF DETECTABLE CHANGES IN PERIPHERAL BLOOD. One of the main goals of our work was to develop biomarkers that can be easily measured in blood that reflect changes in the bone marrow. We therefore explored the possibility whether the proteins that are significantly differentially expressed in bone marrow will also show similar expression pattern in peripheral blood. With this in mind, we calculated how many of the 164 differentially expressed proteins in peripheral blood and the 138-protein dataset in bone marrow are common to both body compartments. We found that only 57 proteins (approx. 30%) of these proteins were in common between the two 164 and 138 datasets as described above. This set of 57 proteins was then subjected to unsupervised hierarchical clustering analysis. All sample groups were distinctively separated into four response subtypes using unsupervised hierarchical cluster analysis as illustrated in the figure below.

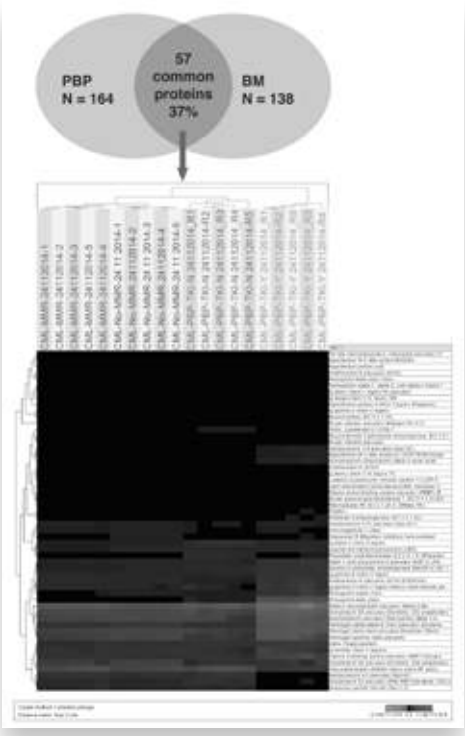


Figure 9: Unsupervised Hierarchical cluster analysis 57 identified differentially expressed proteins that are common in both bone marrow plasma (dataset of 138 proteins) and peripheral blood plasma (dataset of 164 proteins) of CML samples. The dendrogram shows correct prediction of patients with long-term Major Molecular Response (LT-MMR, green), persistent No-Major Molecular Response (P-NoMMR, blue), patients that stay on TKI after 1year of Imatinib Rx (purple) and patients on alternative treatment outside TKI (red). The figure was generated using J-Express software program.

CONCLUSION

We have identified protein signatures capable of prediction of molecular response and choice of therapy for CML patients at 6 months and beyond using expression proteomics as objective stratification of CML patients for treatment options.

Although these results are very promising, we recognized that analysis of much larger materials of patients with similar treatments and responses will be necessary to validate if clustering analysis can be used as a routine prognostic tool for CML patients.

These proteins might be valuable once validated, to complement the currently existing parameters for reliable and objective prediction of disease progression, monitoring treatment response and clinical outcome of CML patients as a model of personalized medicine.

A manuscript has been submitted to British Journal of Cancer, Dec 2015, status as under consideration.

PROJECT TITLE: Investigating the Role of the Actin Bundling Protein (Fascin) in Regulating Dendritic Cell Migration and Breast Cancer Metastasis in Saudi Population
RAC # 2060 016

PRINCIPAL INVESTIGATOR: *Dr. Monther Al-Alwan*

CO-INVESTIGATORS: *Dr. Hazem Ghebeh, Dr. Asma Tulbah, Dr. Taher Tweigeri, Dr. Dahish Ajarim, Dr. Mahmoud Al Jurf*

PROJECT DESCRIPTION: Despite success in treatment of breast cancer, mortality remains high mainly due to chemoresistance and metastasis. Fascin is an actin-bundling protein that has been reported to regulate cell's morphology and motility. It has restricted expression in specialized normal cells, but fascin expression was observed in various transformed cells including breast cancer. The exact role of fascin in breast cancer cells has not been fully understood. The main aim of this proposal is to examine whether fascin induction in breast cancer facilitates metastasis and delineates the underlying mechanism.

PROGRESS/ MAJOR FINDINGS:

1. Four (4) abstracts were submitted to national and international meetings:
   - Revealing a novel regulator of breast cancer stem cells: implication for targeted therapy. Alfaisal University, Riyadh Saudi Arabia.
   - Stem Cells in Health and Disease. Baku World Forum of Young Scientists, Baku, Azerbaijan.
   - The role of actin cytoskeleton in the function of Breast cancer stem cells. The 2013 Annual Research Report, Riyadh, Saudi Arabia.
   - Novel role for fascin in regulating the function of breast cancer stem cells. Stem Cell and Cancer, Banff, Alberta, Canada.

2. One (1) manuscript was submitted and accepted:
   - Ghebeh H, Alkhaldi S, Olabi S, Alkhaldi S, Al-Dhfyan A, Al-Mohanna F, Tulbah A, Al-Tweigeri T, Ajarim D Al-Alwan MM. Fascin is involved in the chemotherapeutic resistance of breast cancer cells predominantly via the PI3K/Akt pathway. [British Journal of Cancer. 111, 1552–1561. doi:10.1038/bjc.2014.453]. This manuscript has been highlighted in Mammary Cell News. (http://www.mammarycellnews.com/issue/volume-6-31-aug-14/)

3. Four (4) oral presentations, 1 of them at an international conferences:

- Revealing a novel regulator of breast cancer stem cells: implication for targeted therapy. Alfaisal University, Riyadh, Saudi Arabia. (invited speaker- November 26, 2014)
- Biology of Stem Cells. Future Scientist Summer Program. King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. (Invited speaker- June, 2014).
- Stem Cell Research in Saudi Arabia: King Faisal Specialist Hospital and Research Center Experience. Baku World Forum of Young Scientists, Baku, Azerbaijan (invited speaker- May 26th- 31st, 2014)
- The role of actin cytoskeleton in the function of Breast cancer stem cells. The 2013 Annual Research Report, Riyadh, Saudi Arabia (keynote speaker- April 2nd-3rd, 2014)

4. Ongoing work established significant relationship between fascin and stem cell phenotype and function.
5. Two manuscripts are in preparation for submission.

PROJECT TITLE: Characterization of Fascin Role in Stem Cell Function Using a Knockout Mouse Model
RAC # 2130 017

PRINCIPAL INVESTIGATOR: *Dr. Monther Al-Alwan*

CO-INVESTIGATORS: *Dr. Hazem Ghebeh, Dr. Ayodele A. Alaiya, Ms. Rayanah Barnawi, Dr. Falah Al-Mohannah, Dr. Asma Tulbah*

PROJECT DESCRIPTION: Our work on human breast samples has established a role for fascin in regulating chemoresistance and metastasis of breast cancer cells. In addition, work in progress has shown a direct role for fascin in regulating the expression and function of breast cancer stem cells, a small subset of breast cancer cells that are widely believed to be responsible for tumor relapse and metastasis. The main aim of this proposal is to establish a fascin knockout mouse model in order to understand the role of fascin in stem cell development and function under physiological conditions.

PROGRESS/MAJOR FINDINGS:

1. Fascin knockout mouse has been generated.
2. Genotyping protocol has been established to differentiate between wild type, heterozygous and homozygous.
3. Flow cytometry setting has been optimized to characterize stem cells from breast and bone marrow as well as immune cells from spleen, lymph node, thymus and blood.
4. RT-PCR optimization is ongoing to characterize key genes in stem cell development and function.

PROJECT TITLE: NSTIP/BIOTECH 12-BIO2342-20: Proteomic Analysis of Lupus Nephritis

PRINCIPAL INVESTIGATOR: *Dr. Mamdouh Albaqumi*
CO-INVESTIGATORS: *Dr. Ayodele Abdulkareem Alaiya, Dr. Khaldoun Alromaih*

PROJECT DESCRIPTION: Lupus Nephritis (LN) is one of the most common causes of renal failure in Saudi Arabia. Treatment and prognosis in lupus nephritis were based mainly on the findings in renal histopathology obtained by renal biopsy. Although renal biopsy is the gold standard in diagnosing glomerular disease including lupus nephritis, it is an invasive procedure with potential serious complications. Given the disconnect between the pathogenic mechanism and the disease phenotype, as well as the risks involved with kidney biopsy as an invasive procedure, a robust non-invasive tool is needed to identify new pathogenic markers that can distinguish between two different kidney diseases with different underlying etiologies but manifest with the same

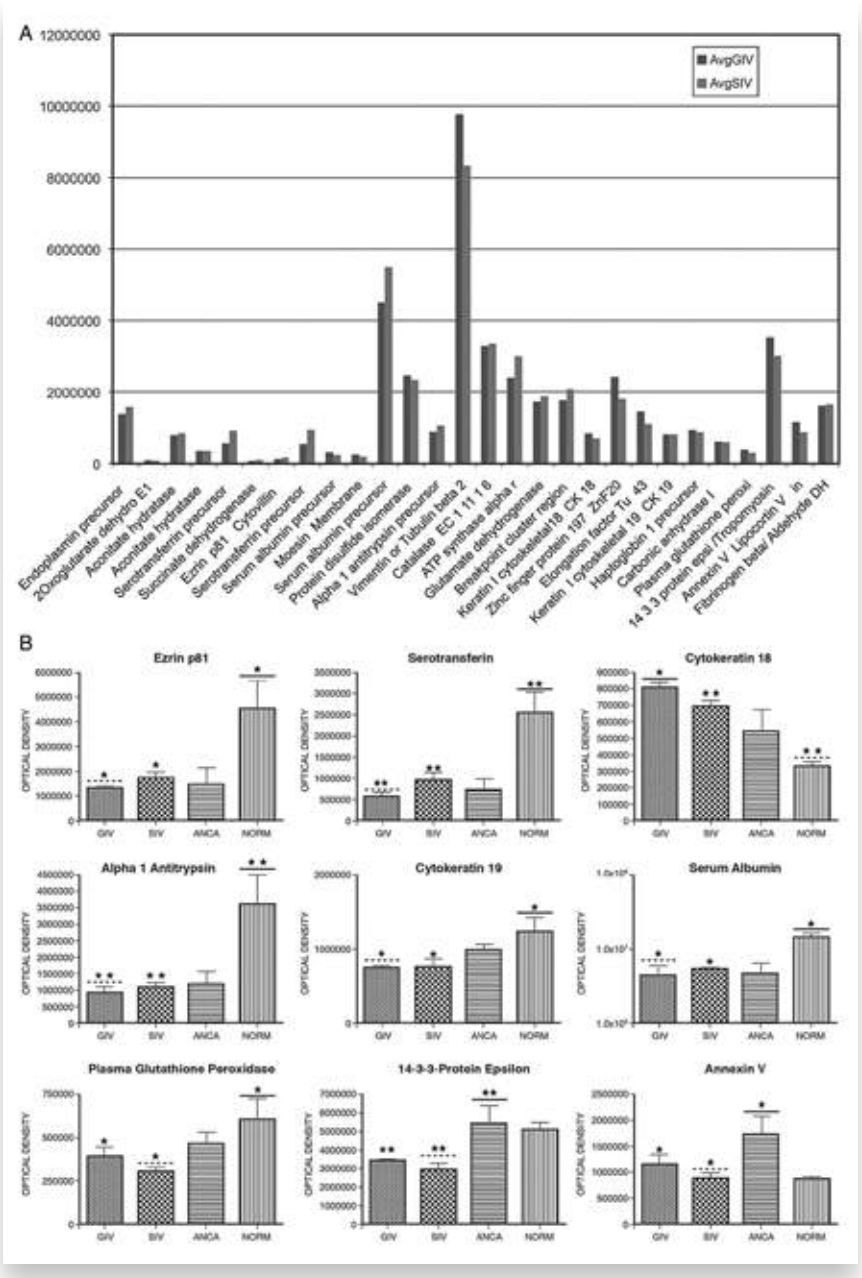


Figure 10. **(A)** Quantitative comparison of identified proteins expression between IV-G (blue) and IV-S (red) showing high degree of similarity between the two sample groups. **(B)** Below are histograms representing expression changes between IV-G (small chess board) and IV-S (large chess board) versus ANCA (horizontal crossbars) and normal kidney (vertical crossbars). The plot was generated using the expression dataset of some of the polypeptides that show similar expression profiles between IV-G and IV-S but differs significantly to ANCA and/or normal. Bars mark statistically significant differences among the sample groups. The histograms represent the means of normalized optical density of protein expression ± standard deviations. The lowest group means (broken bar) and highest group means (solid bars) were indicated, while *indicates statistical difference with P-value < 0.05 and **indicates P-value < 0.005)

histopathology. This will be critical to both guide treatment, as well as to identify new therapy. Over the past decade, proteomics has emerged as a powerful tool in mechanistic, diagnostic, and therapeutic application. One major limiting factor in proteomics studies in renal disease is the availability of enough tissue/serum/urine materials with adequate and reliable clinical data. To overcome such obstacle, we are creating of a bio-bank, where all tissue samples/serum/urine are complemented with complete clinical data. This will be the infra-structure for any future studies in kidney diseases. The other limiting factor was using urine alone which would make identifying a potential biomarker cumbersome and tracing it back to its site of origin very difficult. In this project, we are combining proteomics data from the kidney biopsy of lupus nephritis with urine of the same patient at the time of the biopsy. This will identify potential markers that exist in both tissue and urine eliminating nonspecific proteins that leak out as a result of renal failure. This study will be the first work to use combined tissue/urine proteomics in lupus nephritis and it will bring together basic scientists and clinicians towards discovery of novel biomarkers for routine diagnostics. It will ultimately result in the establishment of center of excellence for clinical proteomics and genomics research with potential for clinical application in routine patient care in Saudi Arabia.

PROGRESS: We found that there is no strong evidence to support a different outcome between the two subcategories of Class-IV LN and, they should thus be treated the same until further studies indicate otherwise. The above work gave insight that these proteomic quantitative datasets are of interest as potential diagnostic markers and can offer an alternative complementary objective approach towards molecular classification of LN. Additionally, and based on this work, one might question the benefit of the Class IV subcategories (global and segmental) sub-classification to either predict prognosis or guide therapeutic decisions.

Our findings on this project are detailed in a recently published paper titled: Proteomic analysis of Class IV lupus nephritis (Alaiya et al; Nephrol Dial Transplant, 2015. 30: 62–70).
http://www.ncbi.nlm.nih.gov/pubmed/24914093

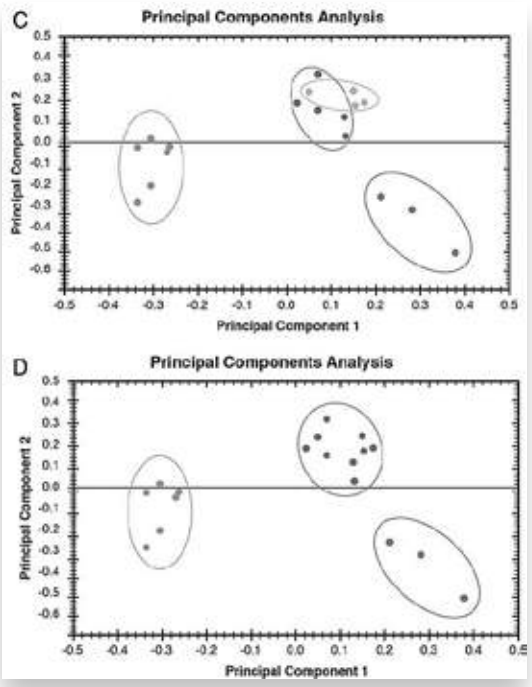


Figure 11. A panel of dataset of 72 polypeptides that were significantly differentially expressed (ANOVA, $P < 0.05$ and ≥1.8-fold-changes in expression levels) was subjected to principal component analysis (PCA) of all the sample groups. Interestingly the LN samples were classified into dour clusters with two distinct and two overlapping as Global Class IV (IV-G—pink, Segmental Class IV (IV-S)—blue, ANCA—purple and normal kidney—orange). (D) However; we observed a distinct classification into three clusters when IV-G and IV-S are merged as one group (blue) and compared with ANCA-vasculitis (yellow) and normal kidney tissue (purple) indicating that IV-G and IV-S could be described as one entity. This type of analysis allows an objective sample classification and identification of outliers in sample groups based on quantitative expression profiles. (Source: Alaiya et al Nephrol Dial Transplant (2015) 30: 62–70.

PROJECT TITLE: Proteomic Analysis of Lupus Nephritis and Other Kidney Diseases
RAC#- 2140-014

PRINCIPAL INVESTIGATOR: *Dr. Ayodele Abdulkareem Alaiya*
CO-INVESTIGATORS: *Dr. Mamdouh Albaqumi, Dr Turki Alhussein, Dr. Khaldoun Al-Romaih*

SUMMARY: Lupus nephritis is one of the most common causes of renal failure in Saudi Arabia. Treatment and prognosis in lupus nephritis were based mainly on the findings in renal histopathology obtained by renal biopsy. Although renal biopsy is the gold standard in diagnosing glomerular disease including lupus nephritis, it is an invasive procedure with potential serious complications. Given the risks involved with kidney biopsy as an invasive procedure, a robust non-invasive tool is needed to identify new pathogenic markers that can distinguish between two different kidney diseases with different underlying etiologies but manifest with the same histopathology. This will be critical to both guide treatment, as well as to identify new therapy.

This study will be the first work to use combined tissue/urine proteomics in lupus nephritis and to bring together basic scientists and clinicians towards discovery of novel biomarkers for routine diagnostics. It will ultimately result in the establishment of center of excellence for clinical proteomics research with potential for clinical application in routine patient care in Saudi Arabia.

AIMS

1. To establish registry database and storage of tissue repository of kidney disease
2. To conduct combined tissue /serum/urine proteomic analysis in lupus nephritis
3. To validate potential biomarkers

PROGRESS: In the second half of 2015 we resumed patient recruitment and bio-sample storage (-80C); towards the building of the proposed kidney biobank, including frozen kidney biopsy (extra material after collecting the biopsy for diagnostic work-up), Serum, sample, and urine sample. We have also collected white blood cells (for DNA/RNA extraction) of LN patients, in addition to expanding the study to include other Kidney diseases. Altogether we have more than 50 recruited patients into the registry prospective blood and urine samples as well as some archived bio-samples (Table below).

Currently optimization of urine processing is ongoing and it is anticipated sample proteomics and genetics analysis would soon follow suit.

Lupus Nephritis and Other Kidney Diseases Bio-Bank Data Sheet

L.N. Sample	Gender	Date of consent	Analysis	Notes
L.N #1	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #2	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #3	Male	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #4	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #5	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #6	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #7	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #8	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #9	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #10	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished

L.N. Sample	Gender	Date of consent	Analysis	Notes
L.N #11	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #12	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #13	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #14	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #15	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #16	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #17	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #18	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #19	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #20	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #21	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #22	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #23	Male	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #24	Female	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished
L.N #25	Male	Retrospective	Mass Spec/ Proteomics	Used for publication/ sample is finished

The previous samples were used for the first paper. New samples for the second paper (ongoing) are shown in the following table.

L.N. Sample	Gender	Date of consent	Blood Sample	Urine Sample	Biopsy	
					OCT Date	Receive Date
L.N #1	Female	Sep-07-2015	Oct-26-2015	Oct-26-2015		
L.N #2	Male	Oct-25-2015	Dec-30-2015	Oct-25-2015	Sep.2015	Jan-26-2016
L.N #3	Female	Oct-26-2015	Oct-26-2015		Sep.2015	Jan-26-2016
L.N #4	Male	Nov-01-2015	Nov-01-2015	Nov-1-2015		
L.N #5	Female	Nov-23-2015	Nov-23-2015	Nov-23-2015	Sep.2012	Jan-26-2016
L.N #6	Female	Nov-23-2015	Nov-26-2015	no urine	Sep.2015	Jan-26-2016
L.N #7	Female	Nov-24-2015	Dec-03-2015	no urine	Sep.2012	Jan-26-2016
L.N #8	Female	Dec-06-2015	Dec-07-2015			
L.N #9	Male	Dec-07-2015	Dec-07-2015	Dec-07-2015		
L.N #10	Male	Dec-13-2015	Dec-13-2015	Dec-13-2015	Sep.2012	Jan-26-2016
L.N #11	Male	Dec-14-2015	Dec-15-2015	Dec-15-2015	Sep.2014	Jan-26-2016
L.N #12	Male	Dec-27-2015	Dec-27-2016	Dec-27-2016	Sep.2013	Jan-26-2016
L.N #13	Male	JAN-03-2016	JAN-03-2016			
L.N #14	Female	JAN-04-2016	JAN-04-2016	JAN-04-2016		
L.N #15	Female	JAN-10-2016	JAN-10-2016			
L.N #16	Female	JAN-11-2016	JAN-11-2016	JAN-11-2016		
L.N #17	Male	JAN-17-2016	JAN-17-2016	JAN-17-2016		
L.N #18	Male	JAN-17-2016	JAN-17-2016	JAN-17-2016		
L.N #19	Male	JAN-19-2016	JAN-19-2016	JAN-19-2016		
L.N #20	Female	JAN-24-2016	JAN-24-2016			
L.N #21	Male	JAN-24-2016	JAN-24-2016	JAN-24-2016		

PROJECT TITLE: Transcriptional Regulation of Podocyte Gene Expression, and Podocyte Injury
RAC# 2150-010

PRINCIPAL INVESTIGATOR: *Dr. Khaldoun Al-Romaih*
CO-INVESTIGATORS: *Dr. Mamdouh Albaqumi, Dr. Ayodele Abdulkareem Alaiya*

PROJECT DESCRIPTION: Podocyte injury is a landmark of glomerular disease/nephrotic syndrome. Transcriptional regulation of podocyte gene expression has been implicated in human and animal proteinuria. Experimentally induced nephrosis by puromycine aminonucleoside (PAN) is generally used as a model for podocyte injury and the onset of proteinuria. PAN responsive genes have been suggested as useful tools for effective screening of early renal injury, indicating their usefulness as disease biomarkers. Targeted gene studies have identified a few genes with transcription regulation function in the context of podocyte biology and injury. Mutations in WT1, a transcription factor and a member of the zinc finger family of proteins, have been reported in patients with nephrotic syndrome. Expression of other zinc finger proteins has been suggested to mediate response to PAN. The nuclear transcription factor and zinc finger protein znf268 has been reported to mediate NF-kB and NF-kB activation has been associated with the onset of proteinuria. This study Aims to 1) Analyze the detailed mechanism of znf268-NFkB interplay of nephrosis/podocyte injury utilizing the nephrosis drug PAN and 2) Study the bulk changes in gene/protein expression of podocytes and in a PAN treated human podocyte model. These changes will be perceived as early landmarks in progression to NS and ultimately serve to initiate future studies to identify their usefulness as diagnostic tools.

PROGRESS AND PRELIMINARY FINDINGS:

1. To pursue our scientific goals in this project we acquired an immortalized human visceral epithelial cell line with the capacity to differentiate to wt1- and synaptopodin-expressing podocytes (collaboration with Dr Salim Moin, University of Bristol, UK). We propagated and archived this cell line in our lab and characterized it using multiple antibodies specific for podocyte including wt1, cd2ap and synaptopodin. Since this cell line has the capacity to differentiate to podocytes we investigated whether nehron progenitor cell markers are expressed including nanong, oct4, and sox2 (Figure 12A). Then, we profiled the expression and localization of zinc finger protein 268 (ZNF268) in podocytes and analyzed its response to PAN as a mean to set a biological indicator for performing a global gene and protein expression analysis. Our initial analysis indicated the expression of ZNF268a and ZNF268b in podocytes with both cytoplasmic and nuclear localization (Figure 12B,C and D).
2. Since our goal is to study gene regulation of podocyte injury and ZNF268/NFkB pathway outside the context of cell death/apoptosis, we have conducted a series of experiments to identify the sub-lethal doses of PAN in differentiated podocytes. We found PAN doses at a final concentration above 25 ug/ml to cause significant cell death/apoptosis while PAN at final concentration of 20 ug/ml and below resulted in no marked death/apoptosis when compared to no-treatment control (Figure 13A). Subsequently, we used an NFkB-GFP reporter assay (a gift from Dr Abu Khabar's laboratory) to measure the effect of the sub-lethal doses on NFkB expression in human epithelial kidney cell line HEK293 (Figure 13B).

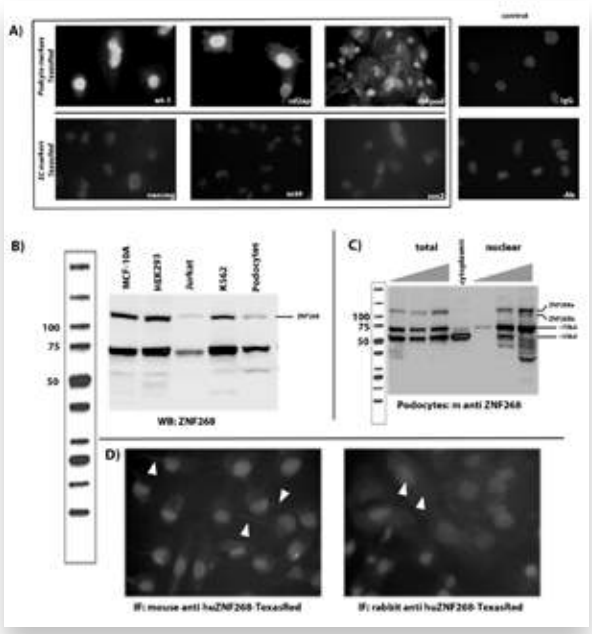


Figure 12. Expression of podocyte markers as indicated by red fluorescent dye 'TexasRed' (**A**, top panel) but not nephron progenitor markers (**A**, bottom panel) in podocytes indicate the biological relevance of these cells as best representative of visceral epithelial cells with the capacity to differentiate to podocytes. Protein expression of ZNF268 in multiple immortalized cell lines (**B**). Cell fractionation followed by western blotting (**C**). The triangle indicates 'mild' to 'harsh' lysis buffers used. Immunofluorescence with different antibodies against ZNF268 in differentiated podocytes.

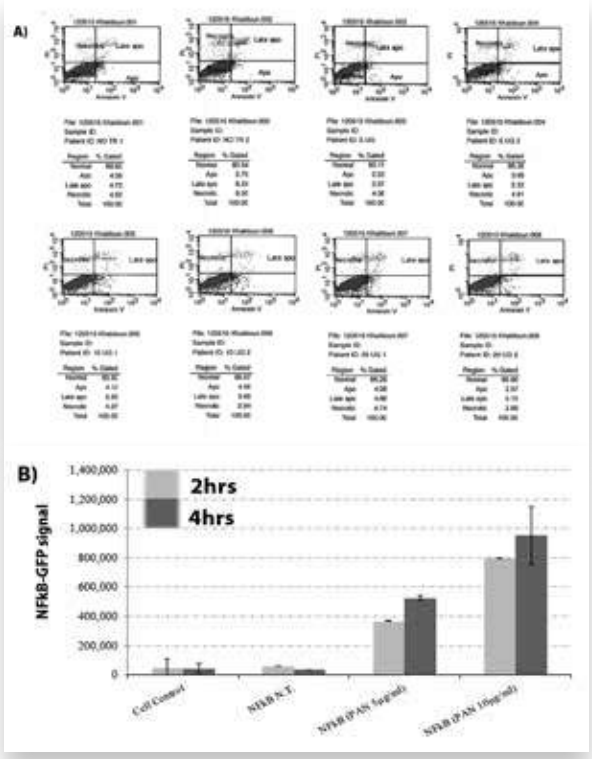


Figure 13. (**A**) AnnexinV/PI analysis by flowcytometery to measure the extent of cell-death/apoptosis in podocytes after treatment with 5, 10, and 20 ug/ml of PAN. The measurement was done 12 hrs after the start of the treatment. (**B**) NF-kB activity as measured by NF-kB-GFP assay 2, and 4 hours after treatment with sub-lethal doses of PAN.

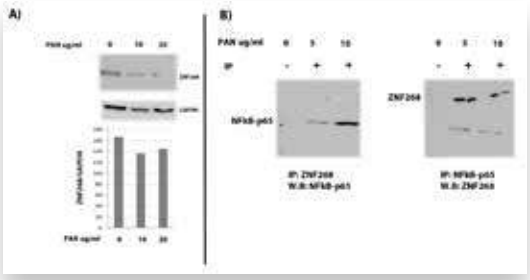


Figure 14. (A) immune blotting of ZNF268 after treatment of HEK293 cells with increasing doses of PAN. The paragraph shows relative expression after normalizing to the loading control GAPDH (analysis was done by ImageJ software). (B) co-immunoprecipitation of ZNF268 and NFkB in the context of PAN treatment (left panel) and the flip experiment (right panel).

PROJECT TITLE: Development and Validation of Proteomics Biomarkers from Human Cerebral Cortex for Diagnostic and Prognostic Management of Epileptic Patients
RAC 2141-035

And

NSTIP/BIOTECH-13-BIO1486-20- Development and Validation of Proteomics Biomarkers from Human Cerebral Cortex for Diagnostic and Prognostic Management of Epileptic Patients

PRINCIPAL INVESTIGATOR: *Abdulaziz Al Semari, MB.BS, PhD*
CO-PRINCIPAL INVESTIGATOR: *Ayodele Abdulkareem Alaiya, MB.BS, PhD, FRCPath*
CO-INVESTIGATORS: *Salah Baz, MD, Hisham Aldalaan, MD, Ibrahim Al Thubaiti, MD, Faisal Alotaibi, MD, Hendi ALhendi, MD*

SUMMARY: Epilepsy syndromes presents with high degree of heterogeneity of disease entities with varied pathologies and clinical sequel. Pharmacoresistance is most common in approximately 30% of patients with epilepsy of structural or metabolic origin, abnormal brain imaging findings and failure to respond to the first two antiepileptic drugs. While definitive epilepsy diagnostic protein-biomarkers are lacking, it is difficult to predict treatment response or surgery outcome due to lack of blood or tissue markers.

This study aims to analyze tissue biopsy, peripheral blood, and CSF from the same individual epileptic subjects for discovery of disease-specific biomarkers using expression proteomics platforms (2-DE and LC/MS/MS).

Results from this study will lead to identification of disease related or tissue-specific proteins that could be potentially useful as disease biomarkers. It will ultimately accelerate the establishment of center of excellence for clinical proteomics research to fast track the path of translational research to clinical application in routine patient care in Saudi Arabia.

AIM: The overall aim of this proposal is the integration of proteomic studies with clinical and pathological parameters carried out at two complementary units of proteomics Research center and Neurosciences Department of KFSHRC, for the purpose of development of diagnostic and prognostic biomarkers for clinical applications for epilepsy.

THE SPECIFIC OBJECTIVES

1. Establishment of bio-bank repository and protein profile changes in brain tissue, peripheral blood, and cerebrospinal fluid (CSF) of mesio temporal lobe sclerosis and focal cortical dysplasia using high-through-put expression proteomics for discovery of disease specific biomarkers.
2. Understanding the relationship between clinico-pathological variables and global protein signatures of mesio temporal lobe sclerosis and focal cortical dysplasia and to use that for differential diagnosis of other types of epilepsy syndromes in a resource pool database for clinical use.
3. Validation and transfer the methodology developed into an expert artificial intelligence

system for more object disease diagnosis and accurate prediction of prognosis and individualized tailored therapy.

PROGRESS: We have so far collected 41 samples of which some were tissue and blood from the same individual, while are only one sample types as tissue or peripheral blood.

There were initial stalling in sample collection has largely due to renovation work in the main operation theatre thus resulted in postponement on many scheduled surgeries, hence the number of analyzed were limited to only 8. There were significant improvements in sample accrual after the renovation work was completed. However, we have not been able to analyze other samples as we were planning to validate four (4) different commercially available plasma depletion kits; and select the most efficient one of the 4 that would subsequently be used for pre analytical removal of the 10 most abundant plasma proteins. This would allow us to analysis of low abundant plasma proteins following the depletion process.

The results of the 8 analyzed samples would be presented in this report and detailed analysis data would follow in the next approval period.

The 8 analyzed samples were classified into three groups including ganglioglioman n=3 and n=2 at median age 12 and 2 years respectfully as well as 3 cases of oligoastrocytoma at median age of 40 years. Altogether we have identified 1633 unique protein species by LC/MS/MS analysis. Expression profiles of 215 significantly differentially expressed proteins classified the samples in distinct 3 clusters. Further analysis indicates that a good numbers of identified proteins in the tissue were among some of the identified proteins in plasma giving the likelihood of discovery of disease-specific biomarkers.

EXPRESSION PROTEOMICS ANALYSIS: Proteomic analysis and changes in protein expression between brain tissues of different histology types from different age groups

We have used a label-free MS-based as a tool for quantitative and comparative expression analysis to analyze protein changes in brain tissue and plasma samples. Approximately > 1630 proteins were detected. We have searched for significantly differentially expressed proteins between the three sample groups ($p<0.001$, at least > 2-fold change and a power of at least > 0.9) and revealed 215 proteins with ~3% false discovery rate (a statistical analysis method used for correction of multiple comparisons, adjusting observed p-values to avoid 'over interpretation' of the significance of the observed results).

Using unsupervised principal component analysis, the 215 significantly differentially expressed protein dataset was able to separate the samples into three distinct clusters groups (Figure15). Interestingly, there seems to be differences between the ganglioglioman of 12 and 2 years average age groups. Whether or not this is significant would be interesting to prove when all clinical details and patient outcome were evaluated in larger sample cohorts as the project progresses into the second year.

The dataset of 215 proteins were subjected to Ingenuity Pathway Analysis (IPA) to evaluate whether some of them were implicated in pathway networks of any neurological conditions. Only 95 of the 215 protein dataset were charted in the IPA database and were found to be represented in multiple different networks of which only one was found to be of particular relevance involving cell death and survival, behavior and metabolic disease (Figure 16).

Furthermore, we explored the disease relatedness or functional annotations of these molecules includes growth and elongation of axions, growth and length of neuritis, mobility of brain, cancer cells lines, and myelination of oligodendrocytes. Others are outgrowth of neuritis, priming of dorsal root ganglion cells, and regeneration of central nervous system as illustrated in Figure 17.

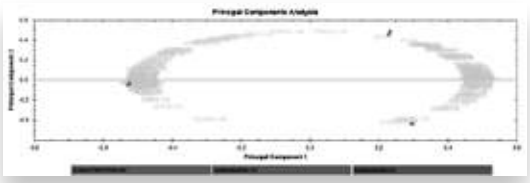


Figure 15. (A) Principal Component Analysis using the 215 identified proteins with significant difference in expression (combined P< 0.001, 2-Fold change and Power 0.9) between different age matched histological epilepsy types. Their expression changes allow for clear separation into three distinct sample clusters. The numbers of the identified proteins are indicated in the grey color, while purple = ganglioglioman- 13 years average age, orange = ganglioglioman- 2 years average age and blue, = oligoastrocytoma- 41 years average age. (The PCA plots were generated using the Progenesis LC-MS (Nonlinear Dynamics, UK).

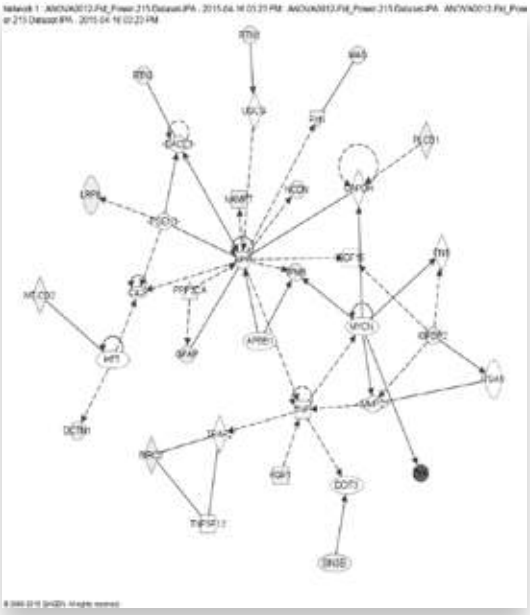


Figure 16. Network pathway involving Cell death and survival, behavior and metabolic disease. (The figure was generated using Ingenuity Pathway Analysis (IPA).

Figure 17. The diseases relatedness or functional annotation of some of the identified proteins were mapped in Ingenuity database and includes among others: growth and elongation of axions, growth and length of neuritis, mobility of brain, cancer cells lines, and myelination of oligodendrocytes. Others are outgrowth of neuritis, priming of dorsal root ganglion cells, and regeneration of central nervous system. (The figure was generated using Ingenuity Pathway Analysis (IPA).

PROJECT TITLE: Proteomic Profiles in the Context of HER2 Phenotype by Comparing HER2 Amplified Tumor to Tumor without HER2 Amplification: Implications for Efficacy of Targeted Therapies
RAC# 2150 005

PRINCIPAL INVESTIGATOR: *Dr. Taher Twegieri*
CO-INVESTIGATORS: *Dr. Abdulkareem Alaiya, Ms. Zakia Shinwari*

AIM: This study aims to analyze peripheral blood, from twenty HER2+ and HER2- breast cancer patients for discovery of disease specific biomarkers using expression proteomics platform of quantitative label-free and high definition liquid chromatography tandem mass spectrometry (LC/MS/MS). The differentially expressed proteins from plasma samples would be validated in large archival materials for their clinical utility.

Results from this study will lead to develop a molecular scanner (artificial intelligence tool) capable of assisting clinical decision-makings in establishing a more accurate diagnosis and prognosis towards achieving personalized medicine for triple negative breast cancer patients.

OBJECTIVES: The main goal of this prospective study is to determine the circulating proteomic profiles of women diagnosed with invasive ductal carcinoma of breast irrespective of the stage in the context of HER2 amplification by comparing HER2 amplified tumor to tumor without HER2 amplification who has not received prior chemotherapy, hormonal or targeted therapy.

PROGRESS

STUDY PHASES

1. Separation of Peripheral blood samples into plasma (PBP) and peripheral blood mononuclear cells (PBMC)
2. Depletion of Peripheral blood plasma (PBP) to remove the 10 most highly abundant plasma proteins
3. Development of learning datasets for objective classification of known Her2 $^{+ve}$ & 10 Her2 $^{-ve}$ cases
4. Analysis of unknown test cases for predictability of learning datasets.
5. Validation of potential protein biomarkers

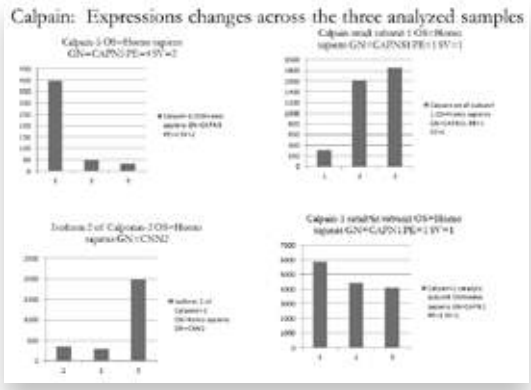
RESULTS: Two samples (Sample #1 and #2) were selected without prior knowledge of their Her2 status. Prior to proteomics analysis the Peripheral blood was separated into (PBP) Plasma and PBMC. Plasma samples depleted to remove the 10 most highly abundant plasma proteins. Altogether > 300 unique protein species were identified from plasma samples and 900 proteins were identified from plasma and PBMC samples respectively.

Both plasma and PBMC samples were subjected to differential analyses

PBMC: 300 identified proteins were significantly differentially expressed (> 2- ∞- folds change, p < 0.005) between Sample-#1 (? Her2 $^{+ve}$), sample #2 (? Her2 $^{+ve}$)

The 300 protein dataset was subjected to principal component analysis (PCA), and the two samples were separated into two distinct clusters.

Among the identified proteins is Calpain, a protein with multiple isoforms. We observes a trend in the expression changes of different isoforms of calpain across the three analyzed samples as shown below and detailed analyses of differentially expressed proteins across all samples are ponding.



CONCLUSIONS

- Proteomics holds promise in discovery of novel biomarkers for accurate definition Her2 status in breast cancer patients
- The use of proteomics marker panels is expected to lead to improved specificity and sensitivity compared with the use of single markers.
- Novel biomarkers to complement currently existing parameters for more objective strati-

fication of her 2 phenotypes among breast cancer patients
- These data are preliminary and will be further re- evaluated to validate their potential clinical usefulness.

PROJECT TITLE: Study of the Relationship Between the Genetic Polymorphisms of the Natural Killer Cell Receptor (KIR) Genes and the Outcome of the Hematopoietic Stem Cell Transplantation for Hematological Malignancies in Saudi Arabia
RAC # 2051 001 (KACST: AT-26-03)

INVESTIGATORS: *Mahamoud Al-Jurf, Abdelghani Tbakhi, Ameera Gaafar Mohamed, Khaled Al-Hussein*

SIGIFICANCE AND MAJOR FINDINGS: Haematopoetic stem cell transplantation (HSCT) is the management of choice for patients with refractory malignancies. The finest clinical ending achieved when patients are fully matched with their donor human leukocytes antigens (HLA) but, a significant number of the HSCT patients develop side effects such as a- GVHD or relapse. Recently, a large body of controversial data has been accumulated on contribution of natural killer (NK) cells to graft-versus-malignancy (GVL) effects following HSCT, particularly in the HLA-identical setting. Therefore, we initiated this study to evaluate the influence of KIR and HLA genotypes on the outcome of bone marrow transplantation (BMT) in a cohort of 87 Saudi patients with hematological malignancies and their living related donors. Peripheral blood was used to isolate genomic DNA and the entire individual had their DNA typed using Sequence Specific Primers (SSP) technique for the presence of all the 16 KIR genes and HLA by SBT. Relapse was observed in 32% of which 16% died. Moreover, 32% of the patients deceased and 47% of the total patients encountered GVDH. Similar to most published data, we observed the dominance of the two framework genes 3DL2 and 3DL3 which are present (100%) in all patients and their related donors. We found that the presence of activating KIR in the donor repertoire promoted adverse immune reactivity, whereas the presence of the inhibitory KIR in the patients promoted immune tolerance and favorable transplant outcome. So it is not only one gene one effect but, rather a combination of many KIR genes, which were involved in relapse, acute and chronic GVHD and death. Most noticeable, KIR2DL5B, 2DL2, and 2DS3 were significantly lower whereas; 3DS1 was higher in the donors of the deceased AML patients. Additionally, we observed absence of KIR2DS2 and 3DS1 in AML patients with relapse. Incidence of KIR2DS3 and 3DS1 was measured to correlate positively with chronic GVHD and relapse. Alternatively, donors with B haplotypes and higher incidence of HLA-C2 homozygote confer significant survival benefits to the patients, whereas, HLA-C1 predominant in the deceased patients. Finally, this study presents a further proof that the outcome of bone marrow transplantation is influenced by the KIR repertoire and KIR/HLA interactions. This KIR genotyping in addition, to HLA of donor and patient pairs could contribute significantly to the recognition of patients at high risk for mounting adverse side effects and thus may assist with strategy design of GVHD prophylaxis

PROGRESS: The project was successfully completed and final reports were submitted to KACST and ORA. Moreover, the data gathered from this study is being analyzed and a manuscript is under preparations.

PROJECT TITLE: Determination of the Effect(s) of Polymorphism(s) in Specific Genes Controlling the Immune Responses in Saudi Renal Transplant Patients
RAC # 2041 081 (KACST: AT 25-41)

INVESTIGATORS: *Khalid Al-Meshari, Abdelgani Tbakhi, Ameera Gaafar, Khaled Al-Hussein*

SIGNIFICANCE AND MAJOR FINDINGS: In transplantation, KIR and/or HLA mismatching may lead to NK cell activation. In turn, the activation of NK cells depends on the balance between signals from activating and inhibitory receptors. The purpose of this study was to investigate the effect of KIR/ HLA mismatch and KIR genes on graft outcome in a cohort of 100 Saudi kidney transplant recipients and their living related donors. HLA, KIR and cytokines SNPs within genes encoding IFN-γ, TGF-β, TNF-α, IL-6 and IL-10. genotyping was performed by allele-specific polymerase chain reaction (SSP-PCR). The prediction of NK cell alloreactivity was done based on the "missing ligand" hypothesis. Allograft rejection was observed in 17 (17 %) recipients. Similar to most published data, we observed the dominance of the two framework genes 3DL2 and 3DL3 which are present (100%) in all recipients and their related donors. Higher gene's frequencies (56%, 81%) of the inhibitory and activatory genes; 2DL5a and 2DS4 respectively, were found to be associated with donors with graft rejection, compared to 20% and 50% genes frequencies in donors with no rejections. In contrast, a lower frequency (18%) of activatory KIR gene 3DS1 is detected in donors with no rejection compared to those with rejection (50%). A predominance of AA1 genotype was observed in recipients and donors with stable graft followed by ABC5. In addition, we detected a higher HLA-C2 homozygous in acute rejecting patients compared to patients with stable graft. Moreover, the number of 2DL pos and 2DS2pos having no corresponding ligand was three times higher in controls than the rejected patients. In conclusion, KIR and HLA mismatching and gene frequencies found to have an impact on allograft outcome.

On the other hand, when the cytokines SNPs were correlated with the graft outcome we observed that high IL-10 productivity was positively correlated with transplant rejection. HLA matching will be used as covariates in the model (logistic regression or stratification). A combined effect of the cytokine gene polymorphism and KIR-ligand data is currently being computed to study their combined effect on renal transplant outcome. The significance of these results remained to be determined.

PROGRESS: The project was successfully completed and two final reports submitted and accepted by KACST and ORA. Two (2) abstracts were presented nationally and two (2) internationally. One manuscript was published in Transplant Immunology and the 2nd is being drafted and will be submitted soon.

PROJECT TITLE: BCR/ABL Translocation Status and T-cell Stimulation Capacity of Dendritic Cells Derived from CD34+ and CD34- Bone Marrow Compartments from Patients with Chronic Myeloid Leukemia
RAC#990 029

PRINCIPAL INVESTIGATORS: *Dr. Khaled Al-Hussein, Dr. Hamad Al-Omar*
CO-INVESTIGATORS: *Dr. Ameera Gaafar, Dr. M. Al Jurf, Dr. A. Iqbal, Dr. A. Tbakhi, Dr. Fahad Al-Mohareb*

METHODS: Bone marrow samples were collected from 10 normal donors and 10 Ph chromosome positive patients with CML before treatment. CD34+/ and CD34-/lineage negative cells were obtained from bone marrow (BM) of 10 patients with chronic myeloid leukemia (CML). After 14 days of culture phenotypic analysis was done by flow cytometry. DCs subpopulation with CD1a+CD14- was prepared for FISH. The morphology of the cells was assessed by light and scanning electron microscopy. Mixed lymphocyte reaction (MLR) was performed. A phagocyte was assessed by uptake of fluorescence polybeads by DCs generated from the two different BM compartments.

RESULTS: DCs were successfully generated and differentiated from CD34-/lineage-cells as well as from CD34+/lineage-cells. They measured to carry variable DC surface molecules such as CD86, CD80, CD83, CD40 and HLA-DR. The differentiation and maturation of DCs were followed by inverted microscope for 14 days and DCs typical morphological features were confirmed by EM. Phenotypic analysis showed that percentages of surface molecules expressed on DCs generated from CD34-/lineage-ve cells were higher than their counter parts expressed by the CD34+ lineage-cells in CML but statistically not significant. Functional studies revealed a potent T cell stimulatory capacity and an efficient phagocytosis of fluorescence polybeads by DCs generated from CD34-/lineage-ve cells. DCs generated from CD34-/lineage-cells were found to carry the BCR/ABL translocation.

CONCLUSIONS: Finally, we examined in this study a novel valuable source (CD34-/lineage-cells) for the generation of human DCs. These DC were found be comparable to DC generated from their counterpart CD34+ as they showed potent functional capacity and hold promises in immunotherapy modality. Further studies exploring capacity of DC generated from CD34-/lineage-cells in the presentation of specific tumor antigens to cytotoxic T cells is warranted.

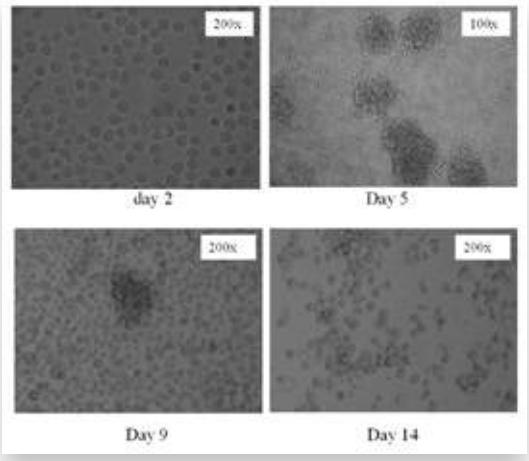
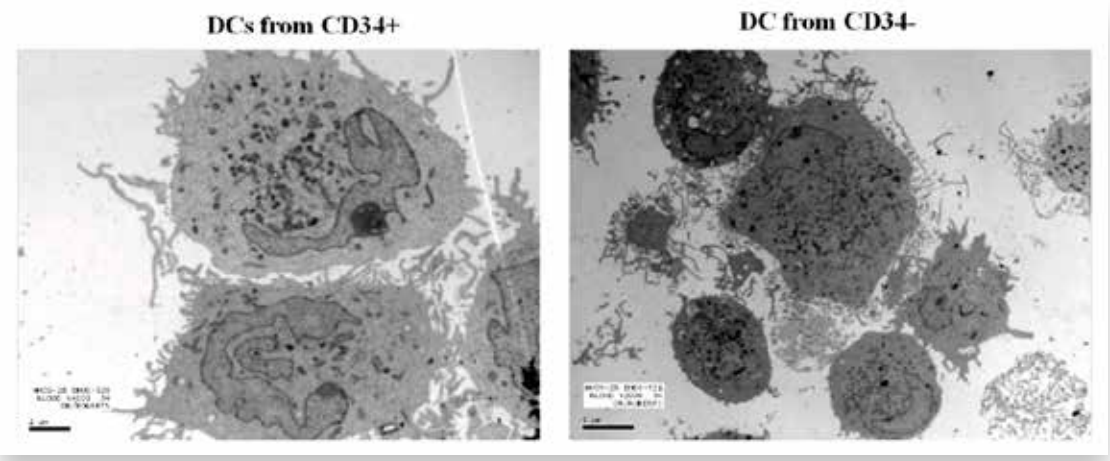


Figure 18. Changes in the morphology of DC from CD34-HPSCs derived from CML patient in 14 days.



PROGRESS: The project was re-activated on the 11th of January 2011. An abstract was published in Exp. Hematol. Two oral presentations presented internationally and two presented nationally and a manuscript was drafted and will be submitted soon.

PROJECT TITLE: Molecular and Immunological Characterization of Dendritic Cells Generated from Primitive CD34 - Hematopoietic Stem Cells in AML & CML Patients: Clinical Applications in Adoptive Immunotherapy
RAC# 2110 007

PRINCIPAL INVESTIGATOR: *Dr. Khaled Al-Hussein*
CO-INVESTIGATOR: *Dr. Chaker Adra, Dr. Fahad Al-Mohareb, Dr. Ameera Gaafar*

SIGNIFICANCE AND MAJOR FINDINGS: Traditionally, hematopoietic stem/ progenitor cells (HSPCs) from bone-marrow or peripheral blood donors are used to cure refractory blood disorders and to influence tolerance in graft-versus-host disease. The most primitive HSCs in mammals comprise the well characterized CD34+ and the rare disused CD34low/- HSCs subsets. However, the defined analysis of the molecular nature of human CD34- and their relation to CD34+ HSCs fractions has been held up by the lack of specific markers. Otherwise, umbilical cord blood has been accepted as an alternative safe source for HSCs; however, the small amount limited its utilization. Therefore, classification of the neglected primitive HSC subsets and identification of an unequivocal marker will facilitate their selection, and propagation in large scale for clinical usage, which eventually will provide cure for more patients in need of HPSC transplantation and positively impact the health care worldwide. This study was intended to provide a thorough analysis using phenotypic and systemic approaches to decipher the cellular and the molecular signature of different HSCs subsets, based on a comparative study combining surface markers and functional ALDH. To our knowledge, this approach has not been adopted before. Lin−CD34−CD38Low/− and Lin−CD34+CD38Low/− HPSC was sorted from UCB and analyzed by flow cytometry real time PCR, and proteomic techniques. Additionally, their multi-differential capacity was assessed *in vitro* by colony forming unit assay. The results revealed distinct biological characteristics of CD34− primitive HSC compartments and hopefully further analysis will facilitate in the discovery of a universal marker(s) and decode the biology of hematopoisis in health and disease.

A pilot study was performed and the proposal was submitted to KACSTs.

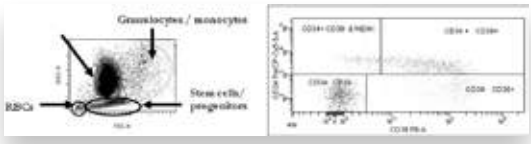


Figure 19. CD34, Lineage-ve and CD38 expression in human bone marrow cells.

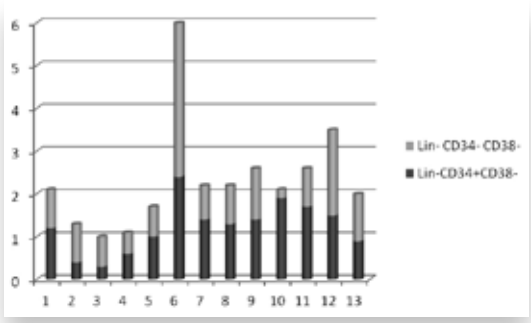


Figure 20. % of Primitive hematopoietic stem/progenitor cell stem cells in cord blood samples.

2015 FULL SCIENTIFIC PUBLICATIONS

PUBLISHED

- Alaiya, A., Assad, L., Alkhafaji, D., Shinwari, Z., Almana, H., Shoukri, M., Alkorbi, L., Ibrahim, H. G., Abdelsalam, M. S., Skolnik, E., Adra, C., Albaqumi, M., Proteomic analysis of Class IV lupus nephritis, *Nephrol Dial Transplant* (2015) 30: 62–70 doi: 10.1093/ndt/gfu215 http://www.ncbi.nlm.nih.gov/pubmed/24914093
- Shinwari JM, Khan A, Awad S, Shinwari Z, Alaiya A, et al. (2015) Recessive mutations in COL25A1 are a cause of congenital cranial dysinnervation disorder. *Am J Hum Genet* 96: 147-152.
- Alsuliman A, Colak D, Al-Harazi O, Fitwi H, Tulbah A, Al-Tweigeri T, Al-Alwan M, Ghebeh H. Bidirectional crosstalk between PD-L1 expression and epithelial to mesenchymal transition: significance in claudin-low breast cancer cells. *Mol Cancer*. 2015 Aug 7;14:149.
- Maayah ZH, Ghebeh H, Alhaider AA, El-Kadi AO, Soshilov AA, Denison MS, Ansari MA, Korashy HM. Metformin inhibits 7,12-dimethylbenz[a] anthracene-induced breast carcinogenesis and adduct formation in human breast cells by inhibiting the cytochrome P4501A1/aryl hydrocarbon receptor signaling pathway. *Toxicology and Applied Pharmacology*. 2015; 284 :217.
- Al-Moghrabi N, Nofel A, Al-Yousef N, Madkhali S, Bin Amer SM, Alaiya A, Shinwari Z, Al-Tweigeri T, Karakas B, Tulbah A. Aboussekhra A, The molecular significance of methylated BRCA1 promoter in white blood cells of cancer-free female. *BMC Cancer*. 2014 Nov 17;14:830. Doi:10.1186/1471-2407-14-830.

2015 ABSTRACTS

INTERNATIONAL SCIENTIFIC MEETINGS:

1. Alaiya A, "Stem Cell Proteomics: Definition of Subset of Breast Cancer Stem Cell-Specific Protein Signatures" Middle East Stem Cell Symposium: Opportunities and Challenges in Stem Cell Research and Therapy Development 24th–25th March 2015 in Doha, Qatar (Invited Speaker).
2. Alaiya AA. Clinical proteomics in oncology-accurate predictions of molecular response in chronic myeloid leukemia (CML) patients as model for personalized medicine, 20th World Congress on Advances in Oncology and 18th International Symposium on Molecular Medicine October 8–10, 2015, Metropolitan Hotel, Athens, Greece (Invited speaker), (http://www.spandidos-publications.com/pages/conference).
3. Ayodele A. Alaiya, Hazem Ghebeh, Ghida Majed Sleiman, Zakia Shinwari, Manogaran Pulicat, Amer Al-Mazrou, Asma Tulbah, Taher Al-Tweigeri, Khaled Al-Faqeeh Identification of novel protein signatures for subtypes of breast cancer stem/ progenitor cells, 14th HUPO 2015 World Congress, taking place September 27–30, 2015 in Vancouver, Canada (Official website: (http://hupo2015.com/) (Oral and Presentations).
4. Ayodele Alaiya, MPH, MBBS, PhD, FRCPath, Hazza A Alzahrani, MD, Zakia Shinwari, MSc, Tarek Owaidah, MD, FRCPA, Fahad Al Mohareb, MD, Fahad Al Sharif, MD, Randa Al Nounou, MD, Naeem A. Chaudhri, MD, FACP, Ghuzayel Aldawsari, MD, Amr Hanbali, MD, Marwan Shaheen, MD, Feras Alfraih, MD, Syed Osman Ahmed, MD, MRCP, FRCPath and Mahmoud

Aljurf, MD, MPH, Molecular Classification of Bone Marrow Failure Syndromes: Protein Signatures as Surrogate Biomarker for Accurate Diagnosis of Severe Aplastic Anemia, Hypoplastic Myelodysplastic Syndrome and Paroxysmal Nocturnal Hemoglobinuria PatientsThe American Society of Hematology (ASH) 57th ASH Annual Meeting in Orlando Florida, December 5–8, 2015 (Official website: (http://www.hematology.org/Annual-Meeting/) Abstract 2414l, December 3, 2015; Blood: 126 (23), (https://ash.confex.com/ash/2015/webprogram/Paper80511.htm)

5. Abdulkareem A. Alaiya, MBBS, PhD, FRCPath, Identification of Novel Protein Signatures as Quality Control in Stem Cell Research; Regenerative Medicine In Orthopedic Surgery 1st International Symposium & Workshop, 18–20 October 2015, King Salman Auditorium, KFSH&RC, Riyadh (Invited Speaker).
6. Ghebeh H, Colak Dilek, Tulbah A, Al-Sulaiman A Towards Targeting PD-1/PD-L1, axis in breast cancer, preclinical data presented at the "Breast Cancer Immunotherapy Symposium (BRECIS), part of Sidra Symposia Series, held in partnership with the Society for Immunotherapy of Cancer" held 13–14 April 2015 in Doha, Qatar.

MEDICAL AND CLINICAL AFFAIRS

DEPARTMENT OF DENTISTRY

DEPARTMENT OF DENTISTRY

CHAIRMAN

Abdulhadi Abanmy, BDS, DMSc

PEDIATRIC DENTISTRY

PROJECT TITLE: Registry of Cleft Lip/Palate and Craniofacial Anomalies
RAC #: 991030

INVESTIGATORS: *Dr. Aziza Al-Johar, Dr. Ali Al Mutlaq, Ms. Shazia Subhani*

PROJECT DESCRIPTION

BACKGROUND: The King Faisal Specialist Hospital & Research Centre(KFSH&RC), established a cleft lip with our without cleft palate (CL/CP) registry and started collecting data on CL/CP patients attending the Department of Dentistry, KFSH&RC since mid-1999. The registry is a coordinated collaboration between the Department of Dentistry and Department of Biostatistics, Epidemiology and Scientific Computing (BESC). The CL/CP registry is being expanded to include craniofacial anomalies in it scope and hence, the name of the registry is being changed from Cleft Lip/Palate Registry to Registry of Cleft Lip/Palate and Craniofacial Anomalies.

RATIONALE: Treatment including multiple surgeries, speech therapy, and dental and orthodontics of cleft lip and palate have developed very rapidly, but the epidemiological study for cleft lip and palate remains in its infancy. The registry is an early warning system for discovering excessive occurrences of craniofacial anomalies and is the foundation for the epidemiological research needed to evaluate the clusters.

KFSH&RC is one of the major referral hospitals in the Kingdom. The development of a Craniofacial Anomalies Registry (in the absence of such a population-based registry) at KFSH&RC will be an important source of data on this congenital defect in the Kingdom.

PROGRESS: On-going project.

PROJECT TITLE: Genetics of Craniofacial Birth Defects in Saudi Arabia
RAC #: 2080006

INVESTIGATORS: *Dr Fouzan Al Kuraya, Dr. Aziza Al Johar*

ABSTRACT: Birth defects are important cause of disability worldwide with tremendous impact on the public health system. Craniofacial birth defects are particularly important because, as a group, they represent the second most common class of birth defects in humans. Additionally, they affect a region in the body that's readily observable by others thereby compounding the psychological component of the disability. The cause of most birth defects is unknown. Genetic, nutritional, infectious, and other environmental factors, contribute to the total incidence of birth defects, but the percentage attribute to each is not known. In Saudi Arabia several factors make it likely that genetic etiologies contribute more significantly to craniofacial birth defects than other parts of the world. Perhaps the most important of these factors is the high frequency of autosomal recessive disorders (many of which will inevitably involve the complex structure of the face and other craniofacial structures) as a result of high degree of inbreeding and consanguinity. One research group has an extensive experience in mapping mendelian disorders, including genetic conditions associated with craniofacial anomalies. Similarly, we have solid expertise in the areas of clinical, molecular and developmental genetics. We propose to focus our existing expertise direction of dissecting the molecular defects

that underline craniofacial birth defects in Saudi Arabia. Characterizing these mutations will have an obvious impact on the medical care of the affected individuals since it makes prenatal/pre-implantation diagnosis available options but it also represents a step in the right direction toward the implementation of gene therapy in conditions that are amenable to this approach. From an academic standpoint, the study of birth defects, craniofacial birth defects included, has proven indispensable to human genetics research. Biomedical literature is replete with high profile examples where the understanding of the genetic etiology of a given birth defect was key to the discovery of highly important genes and pathways that propelled our understanding of how genes eventually control the making of a physical human being. Consequently, our group has a keen interest in understanding how different mutations affect the protein function of the respective genes. Furthermore, new genes identified in the course of this work represent an existing opportunity to better understand the molecular mechanisms that govern the formation of the craniofacial structures by studying their expression pattern and protein function. Given the scope of this project, the methodology will not only include linkage analysis but will also use the latest available tools in developmental and molecular genetics. This is a five year project genetic underlying defect.

AIMS OF THE PROPOSED STUDY

1. To identify the genetic lesions (mutations) that underline the various genetic forms of craniofacial birth defects in the Saudi population.
2. To study the role of the identified genes in the model organism.

PROGRESS: On-going project

PROJECT TITLE: Oral Lesions in Saudi Leukemic Children Following Chemotherapy
RAC #: 2121161

INVESTIGATORS: *Dr Tahani Azizalrahman, Dr. Aziza Al Johar*

INTRODUCTION: Although cancer risk increases with age, malignant diseases are an important cause of morbidity and mortality in children, approximately 1 in 7,000 children between one and 14 years of age in the United States are affected every year.

Statistics have shown that leukemia is one of the 10 most common malignancies amongh pediatric population in Jordan, Leganon, Bahrain, Egypt, Iraq, Libya, Kuwait, Oman, Qatar, Saudi Arabia, Syria and the UAE. In most of these countries, leukemia is also the major form of pediatric cancer (Elsayed et al., 2009).

Intensive chemoradiotherapy damages the mucosal barrier of the mouth and throat and it is often associated with severe oral inflammation and infection, including herpes simplex, candidiasis, mucositis, and gingivitis (Carrega et.a., 1994, Baliga etl al. 1995).

AIMS OF THE STUDY

1. To evaluate oral soft tissue of Saudi children newly diagnosed with acute lymphoblastic leukemia and treated with chemotherapy
2. To evaluate the significance of different independent factors such as (age, gender, educational level of parents, family income, oral hygiene practices, dietary habits and previous dental history) on the oral health status of pediatric patients with acute lymphoblastic leukemia.
3. identify the genetic lesions (mutations) that underline the various genetic forms

of craniofacial birth defects in the Saudi population.
4. To study the role of the identified genes in the model organism.

MATERIAL AND METHODS

STUDY DESIGN: 50 all patients will be examined before receiving the chemotherapy and then one month after the therapy to determine any effects of the chemotherapy on the patients' oral health.

PROGRESS: Final Report

PROJECT TITLE: The Incidence of Oral Mucositis in Pediatric Hematopoietic Cell Transplantation
RAC #: 2091015

INVESTIGATOR: *Dr Zikra AlKhayal, Dr. Mohammed Al Helal, Dr. Abdullah Al Jefri, Dr. Amal Al Seraihi*

PROJECT DESCRIPTION

ABSTRACT: Oral Mucositis is one of the most common and debilitating forms of Mucositis and often arises from high dose chemotherapy and radiotherapy. It is reported that seventy to eighty percent of patients undergoing hematopoietic cell transplantation (HCT) suffer from oral Mucositis during cancer therapy. The objective of the study is to evaluate prospectively the incidence of oral mucositis in pediatric patients aged 0 to 14 years receiving myeloablative conditioning regimens and hematopoietic cell transplantation at the bone marrow transplant unit at King Faisal Specialist Hospital & Research Centre. The results of the study will address the extent of oral mucositis in the bone marrow transplant unit and if there is a need for future management plans to improve the quality of life and provide optimal care for this special group of pediatric patients.

SPECIFIC AIMS AND OBJECTIVES

1. To assess prospectively the incidence of oral mucositis in the pediatric population receiving hematopoietic cell transplantation (HCT) at King Faisal Specialist Hospital & Research Centre-Riyadh.
2. To evaluate the factors predicting oral mucositis severity and correlation with disease category, conditioning regimen, type of transplant and delayed absolute neutrophil recovery.
3. The outcome of oral mucositis and relation between grade severity, reported pain, ability to eat, saliva production and analgesic use.

METHOD: The study will be a prospective cross-sectional, case-control study.

PATIENTS: The sample study population will consist of all pediatric patients age 0 to 14 years old undergoing hematopoietic cell transplantation at King Faisal Specialist Hospital & Research Centre during the study period August 2015-August 2016.

PROGRESS: On-going.

PROJECT TITLE: Stem Cells from Human Exfoliated Deciduous Teeth (SHED): A Stem Cell Source for Bone Regeneration
RAC #: 2110024

INVESTIGATORS: *Zikra Alkhayal, Saleh Al Bazie*

PROJECT DESCRIPTION

SUMMARY: Postnatal stem cells have been isolated from a variety of tissues including but not limited to bone marrow, brain, skin, hair follicles, skeletal muscle, and dental pulp. The dental pulp should be considered as an important site for mesenchymal stem cells. Stem cells from the pulp are pluripotential

and found to be ideal in tissue engineering and for clinical use in several pathologies requiring bone growth and repair the transplantation of newly formed bone obtained from dental pulp stem cells lead to the formation of vascularized adult bone and integration with surrounding tissue. The dental pulp stem cells are usually recovered from recently extracted health teeth, notably deciduous teeth, developing third molars, and other permanent teeth. The properties of stem cells recovered from the pulp of deciduous teeth are different from those found in permanent teeth and have been labeled SHED cells for Stem cells from Human Exfoliated Deciduous teeth. SHED cells have also been shown to be more proliferative than bone marrow stem cells. Further, Stem cells from developing third molars and other developing permanent teeth, e.g. bicuspids removed for orthodontic indications, are also very proliferative.

AIMS & OBJECTIVES

1. Enhance our understanding in isolating, characterizing and differentiating mesenchymal stem cells from three different goups.
   - Stem human exfoliated deciduous teeth (SHED) from healthy subjects
   - Stem human exfoliated deciduous teeth (SHED) from patients with osteopetrosis
   - Stem cells from third molars
2. Compare the osteoblast differentiation of dental pulp stem cells, through specific biological regulation of the healthy group vs the osteopetrotic group.
3. Use the human bone marrow-derived mesenchymal stem cells as our control.

METHODOLOGY: It is hypothesized that dental pulp stem cells including SHED and from third molars from healthy subjects have differentiation lineage that can enhance bone development more than DPSCs from subjects with Osteopetrosis disease.

The stem cells will be derived from the following:

1. Pulp of incisors and canines of healthy subjects 5-15 years of age
2. 2. Pulp of incisors and canines of osteopetrosis subjects 5-15 years of age
3. 3. Pulp of third molars of healthy subjects 17-35 years of age.

PROGRESS: Reactivated started.

PROSTHODONTICS

PROJECT TITLE: Rare Dental Disorder Registry
RAC #: 2071082

INVESTIGATORS: *Dr Adeeb Al Omrani (PI), Dr Mohammed Al Helal, Dr Richard Hakansson, Dr Khalid Al Zoman, Ms Shazia Naz Subhani*

PROJECT DESCRIPTION

ABSTRACT: Congenital Oral Anomalies are a broad category of health conditions that are present at birth and are a deviation from normal anatomic growth, development, or function. There is an urgent need to increase knowledge about oral rehabilitation for people with oral/dental disabilities and new methods for treatment must be developed and evaluated. This will lead to better care and will have great influence on the quality of life for people with oral disabilities.

The aim of this registry is with a multi disciplinary team approach enhancing the opportunities for individuals with rare-oral and facial disorders to get adequate information, diagnosis and treatment at King Faisal Specialist Hospital & Research Center, from all over the country.

PROGRESS: On-going

PROJECT TITLE: Gene Expression & Immuno-Histological Findings in Patients with Papillon Lefèvre Syndrome"
RAC #:2070022

INVESTIGATORS: *Adeeb Al Omrani BDS, DMSc (PI) Namik Kaya, PhD (Co-PI), Saleh Al-Muhsen, MD Dilek Colak, PhD, Hamad Al Zaidan, MD Said Dermime, PhD, Mohammed Al Owain, MD Hazem Ghebeh, PhD, Richard Hakansson, DDS, PhD, Christer Ullbro, DDS, PhD*

PROJECT DESCRIPTION

ABSTRACT: Papillion-Lefebvre syndrome is an autosomal recessive disorder characterized by hyperkeratosis of palm and soles and by a generalized aggressive periodontitis and premature loss of primary and permanent dentition. It is relatively prevalent in a small village north of Riyadh with more than 60 patients being followed in the dental clinic at KFSH&RC. Severe periodontal disease plays an important role in PLS resulting in premature loss of primary and permanent dentition. Two mutations have been identified in the cathepsin C (CTSC) gene in this population. The aim is to study the histopathology, immunological profile, and gene expression of PLS from blood samples and gingival biopsies; and thus shed more light on the pathophysiology of the disease and explore whether new subclasses of this disease can be identified based on gene expression profiles. Furthermore, we aim to establish a preventative program among this high-risk group through carrier testing and genetic counseling. The study will include 40 PLS patients presented at the dental department in KFSH&RC, retrospectively. A correlation may be found between the immunological status/ gene expression and level/severity of periodontal infection. This may give more insight on the role of cathepsin C in the disease.

AIMS: Our aim in this study is to perform a thorough genetic and immunological evaluation in a cohort of Saudi patients with PLS from the following aspects:

4. Comprehensive genetic assessment:
   - Gene expression profiling of PLS patients, carriers and controls in the blood and patients, and controls in gingival tissue.
5. Study the immunologic status of PLS from blood samples:
   - Detailed neutrophils function including: adhesion (by means of CD11/CD18 expression) chemo taxis, phagocytosis and killing abilities (by evaluating the oxidative burst function).
   - Lymphocytes phenotypic distribution, and lymphocytes proliferation assays.
   - Natural Killer cytotoxic activity.

PROGRESS: On-going.

PERIODONTICS

PROJECT TITLE: Serum Levels of Leptin, C-reactive Protein and Pro-Inflammatory Cytokines: Their Relationship to Periodontal Health and Disease in Saudi Periodontitis Patients
RAC#2111065

INVESTIGATORS: *Dr. Khalid Al Zoman, Dr. Fatwan Ak Muhanna, Dr. Ali Al Ghamdi*

PROJECT DESCRIPTION

PURPOSE: The purpose of this study is to investigate the effects of the periodontal treatment on the serum levels of leptin and other cytokines in Saudi patients with chronic periodontitis (CP).

ABSTRACT: Metabolic syndrome is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes (1). Periodontal disease is associated with the components of Metabolic syndrome, such as obesity, diabetes, hypertension and hyperlipidemia. Therefore, strong relation with periodontal disease and metabolic syndrome is suggested. Because both periodontitis and the metabolic syndrome are associated with systemic inflammation and insulin resistance, these two diseases may be linked through a common pathophysiologic pathway (2,3).

Leptin, a non-glycosylated polypeptide hormone, has been classified as a cytokine (4). Leptin and its receptor share structural and functional similarities with members of the long chain helical cytokines: interleukin-6, interleukin-11, interleukin-12, leukemia inhibitory factor, granulocyte-colony–stimulating factor, and oncostatin M (5). Thus, leptin might be classified as a cytokine. Circulating leptin in humans is mainly secreted from adipose tissue (5). It has been suggested that leptin orchestrates the host response to inflammatory and infectious stimuli as it induces the production of cytokines and allows for the phagocytosis of macrophages (6,7). Thus, the overall increase in leptin during inflammation and infection indicates that leptin is part of the immune response and host defense mechanisms.

Several studies have reported an association between severity of periodontitis and leptin levels in serum or gingival crevicular fluid (GCF) (8-10). Karthikeyan et al (9) reported that leptin levels decreased progressively in GCF as periodontal disease progressed.

Recently, it has been suggested that leptin plays a significant role in bone formation by virtue of its direct effect on osteoblast proliferation and differentiation, and in prolonging the life span of human primary osteoblasts by inhibiting apoptosis (10). Leptin is also involved in antiosteogenic effects by acting centrally on the hypothalamus (11). Thus, leptin at high local concentrations protects the host from inflammation and infection and maintains bone levels (12).

PROJECT DESCRIPTION: Adipose tissue secretes pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-6, which are involved in the pathophysiology of obesity and periodontitis (13). It has been reported that obese individuals have elevated levels of circulating TNF- α and IL-6 compared to normal weight subjects, and that levels of these cytokines decrease after weight loss (14). TNF-α and IL-6 are the main inducers of acute-phase hepatic protein production, including C-reactive protein (CRP) (15). In humans, plasma levels of TNF-α, IL-6, and CRP are closely related to obesity and insulin resistance (16,17). Inflammatory diseases like periodontitis induce the production of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 (18,19). It has been suggested that the secretion of TNF-α by adipose tissue triggered by LPS from periodontal Gram-negative bacteria promotes hepatic dyslipidemia and decreases insulin sensitivity (20,21).

MATERIALS AND METHODS

SUBJECTS: A total of 50 CP Saudi patients and 20 healthy subjects will be recruited for this study. Age, gender, smoking status, and body mass index (BMI) will be recorded. The diagnosis of CP will be made according to the classification by the American Academy of Periodontology (22). The CP patients will be recruited from the Outpatient Dental Clinic at King Faisal Specialist Hospital and Research Center, Riyadh. Subjects with >20 teeth present will be selected from

both genders, and those with relevant systemic illnesses, pregnancy, or recent medications will be excluded. All CP patients should not have received any periodontal therapy within the preceding 1 year. Written informed consent will be obtained from all participants before inclusion in the study.

CLINICAL ASSESSMENTS: All subjects (CP and healthy patients) will be evaluated clinically at the first visit to assess the following periodontal measurements: number of teeth, probing depth, clinical attachment level, bleeding on probing, plaque index, and gingival index (GI). Six sites will be examined on each tooth: mesio-buccal, mid-buccal, distobuccal, disto-lingual, mid-lingual, and mesio-lingual.
One trained examiner will take all measurements and record the results.

CP patients will be evaluated clinically after 1 month of periodontal treatment to reassess the periodontal measurements described previously.

PERIODONTAL TREATMENT: CP patients will receive two to 4 visits of oral hygiene instruction and scaling and root planning. Oral hygiene instruction will include the use of interproximal cleaning aids such as floss and interdental brushes. All CP patients will receive scaling and root planing under local anesthesia on a quadrant- by-quadrant basis within 2 months. Scaling and root planing will be performed by sharp sickles and Gracy curets and ultrasonic instruments.

MEASUREMENT OF SERUM LEPTIN, ADIPONECTIN,TNF-A, IL-6, AND C-REACTIVE PROTEIN LEVELS: Levels of leptin, adiponectin, TNF-a, IL-6, and C-reactive protein (CRP) in serum samples will be determined using an enzyme-linked immunosorbent assay (ELISA) kit.

PROGRESS: On-going.

PROJECT TITLE: A Prospective Observational Multicenter Cohort Study to Assess the Incidence of Osteonecrosis of the Jaw (ONJ) in Cancer Patients with Bone Metastases Starting Zoledronic Acid Treatment
RAC#2111094 (S0702)

INVESTIGATORS: *Dr. Waled Rasheed, Dr. Kausar Suleman, Dr. Khalid Al Zoman*

PROJECT DESCRIPTION

PURPOSE: The purpose of the study is to learn how often ONJ occurs in patients who are being treated with zoledtronic acid during a 3-year time period after starting treatment. This study will also identify risk factors associated with ONJ.

OBJECTIVES

1. To prospectively assess the cumulative incidence of osteonecrosis of the jaw (ONJ) at 3 years in cancer patients with bone metastasis receiving zoledronic acid treatment.
2. To describe the clinical presentation and natural history of ONJ.
3. To identify potential risk factors for the development of ONJ.
4. To estimate the cumulative incidence of ONJ at 3 years for different tumor types (breast cancer, multiple myeloma, prostate cancer, lung cancer and other cancers).
5. To investigate potential predictive and/or prognostic markers of increased risk for ONJ and/or to explore the potential mechanism of ONJ, the following correlative science resource banks will be established:
   - A specimen bank of serum for banking and whole blood for DNA analysis
   - A serial imaging bank of available x-rays, scans, CT's and MRI's for ONJ cases, as well as for a set of non-ONJ controls.

6. To better define the patient-related outcomes of ONJ in those patients who develop ONJ.

STUDY DESIGN: This is a SWOG (Southwest Oncology Group) study.

PROGRESS: On-going.

GENERAL DENTISTRY

PROJECT TITLE: A Randomized Phase II Study of Adjuvant Concurrent Radiation & Chemotherapy versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors
RAC#:2111096

INVESTIGATORS: *Nasir Al Rajhi, MD (PI), Mohammed AlGhazi, BDS, Zeyad Mahasin, MD*

PROJECT DESCRIPTION

Determine the feasibility of conducting a cooperative group prospective clinical trial in patients with resected malignant salivary gland tumors;

- Acquire preliminary efficacy data comparing postoperative radiotherapy alone to concurrent chemotherapy and radiation using weekly cisplatin. Secondary Objectives
- Compare the acute toxicities of these 2 adjuvant treatments;
- Compare long-term efficacy results at 5 years and late treatment-related adverse events in patients receiving postoperative radiation to those receiving concurrent chemoradiation;
- Investigate quality of life and patient-reported outcomes in patients enrolled in the study;
- Identify the histopathology and tumor marker expression from patients enrolled on this trial and assemble a tissue bank for future correlative studies;
- Establish an RTOG baseline database for salivary gland malignancies to serve as a resource for future.

PROGRESS: On-going.

PROJECT TITLE: Randomized Phase II Trial of Docetaxal and Cisplatin Versus Low Dose Fractionated Radiation Plus Docetaxal and Cisplatin as Induction Therapy in Locally Advanced Nasopharyngeal Cancer
RAC# 2121063

INVESTIGATORS:, *Nasir Al Rajhi, MD, Mohammed Al Ghazi, BDS, Zeyad Mahasin, MD*

PRIMARY END POINTS

- To assess the efficacy of low-dose RT given in combination with induction chemotherapy (Docetaxal and Cisplatin) in patients with locally advanced Nasopharyngeal cancers by measuring clinical Complete Response(RECIST Criteria) at the primary site. Also, monitor the response with the lymph nodes and Overall Response Rate will represent the total complete response at both sites after the induction regimen.
- Tolerability: The revised NCI (CTCAE) Version 4.03 will be used to score all chemotherapy and acute radiation (< 90 days) toxicities. Late radiation morbidity scored using RTOG/EORTC late radiation morbidity scoring /LENT-Soma scheme for events occurring more than 90 days.

SECONDARY END POINTS

- 3 years distant failure, loco regional failure, overall and disease specific survival.

- Progression free survival will be calculated from date of start of treatment till progression relapse date.
- Disease specific survival from date of diagnosis to date of death from disease.
- Overall survival will be calculated from date of diagnosis till the date of death from any causes. Kaplan–Meier Statistical method will be used to calculate survival, using SPSS Version 15 statistical package.

PROGRESS: On-going.

DERMATOLOGY

DERMATOLOGY

CHAIRMAN

Issam Hamadah, MD

THE DEPARTMENT OF DERMATOLOGY MISSION IS TO PROVIDE THE population of Kingdom of Saudi Arabia with the highest quality medical care through comprehensive diagnosis, management and treatment of various dermatological diseases. The scope of services includes phototherapy and laser treatment. The unit has vast experience with cutaneous diseases related to organ transplant, oncology and immunocompromised patients. It has unique experience in the Kingdom in biologic therapy for psoriasis and immunobullous diseases. Another distinctive expertise is the program for cutaneous tumor prevention by repetitive chemical peel for xeroderma pigmentosum patients, combined vascular anomalies and hidradinitis suppurativa.

We had 16 publications in peer reviewed journals in the last 5 years. In 2015, we participated in a multicenter international study, a precedent for our department.

LIST OF APPROVED PROJECTS

PROJECT TITLE: Evaluation of Changes in Quality of Life & Socio-professional Status in Subjects with Moderate to Severe Plaque Psoriasis Treated with Adalimumab in Routine Medical Practice - EQUIPE
RAC# 2151 012
Source of Funding: Abbvie

PRINCIPAL INVESTIGATOR: *Issam Hamadah, MD*

ABSTRACT

Psoriasis is a chronic, inflammatory, systemic disease that affects approximately 2% of European population. Beyond its skin manifestation, there is evidence that moderate to severe psoriasis is responsible for a negative impact on patient's quality of life. Published data confirms that approximately 60% of people with psoriasis reported their disease to be a problem in their everyday life; among most frequent life domains affected are: psychological, social, sexual and occupational functioning. There has been reported different research in the field of Health-Related Quality of Life which quantified the impact of psoriasis on daily functions and activities as well as quality of life to an extent similar to other major chronic diseases such as oncological diseases, diabetes mellitus, and cardiovascular diseases. It is commonly recognized that the stigma associated with visible skin lesions may lead to psychosocial adjustment problems.

In the same time, psoriasis can have a wide range of direct and indirect financial implications. Direct costs for the patient may include physician visits, day treatment, hospitalization and cost of topical or systemic treatment, as an example. The indirect cost to the society may result from the number of days taken off by the ill person, time lost from work, due to hospital admissions, or even unemployment due to psoriasis. In one study, 60% of study participants blamed psoriasis in the preceding years for their time lost from work and 40% expressed that they did not work owing to psoriasis. Therefore both depression and impact on occupational status are two important quality of life domains impacted by psoriasis.

The introduction of biologic therapy almost ten years ago allowed clinicians all over the globe to obtain improvement in clinical outcomes in dealing with psoriatic disease, as well as significant improvements in health-related quality of life in patients with moderate-to-severe psoriasis. Adalimumab, in phase III clinical controlled trials has been shown to generate a positive effect on health-related quality of life in patients with moderate to severe plaque psoriasis.

As current healthcare standards have undergone changes in the past years, due to review of health policies and introduction of health technology assessment practices and due to the fact that up-to-date real-life data with adalimumab are limited within Eastern Europe and Middle East population, the need to establish the impact of adalimumab therapy on patient health-related quality of life in routine clinical practice was identified. Also, as the Health Technology Assessment is increasingly requesting local generated data for patient-reported outcomes, observational studies involving large patient cohort and local pharmacoeconomic data are needed.

In summary, the rationale of this study is to fill the present knowledge gap with respect to real-world data on changes in quality of life in subjects with moderate to severe plaque psoriasis treated with adalimumab for up to 12 months in routine clinical practice. The changes in overall health status,

mental and occupational status of subjects treated with adalimumab will also be examined.

INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory disease. With its early onset – usually between the ages of 20–30—as well as its chronic relapsing nature, psoriasis is a lifelong disease that has a major impact on affected patients and society. Patient with psoriasis face a substantial personal expense, strong stigmatization, and social exclusion.

Plaque-type psoriasis is the most common clinical form of the disease, with a prevalence of approximately 2% in Western nations.1 Like other chronic inflammatory conditions, psoriasis is associated with a specific pattern of co-morbidities that are believed to be at least partially related to the systemic inflammatory nature of this disease. Thus patients, particularly those with more severe disease, may be at increased risk of cardiovascular disease, hypertension, metabolic syndrome, type II diabetes, fatty liver and its consequences, stroke, depression, chronic obstructive pulmonary disease, sleep apnea, and lymphoma. The life expectancy of patients with severe psoriasis, after adjusting for relevant confounding factors, is approximately 3 to 4 years less that in individuals without psoriasis.

AIM

PRIMARY OBJECTIVE

The primary objective of this observational study is to assess changes in quality of life in subjects with moderate to severe plaque psoriasis treated with adalimumab over 12 months in routine clinical practice.

Changes in quality of life will be assessed by analyzing changes in patient reported Dermatology Life Quality Index (DLQI).

SECONDARY OBJECTIVES

The secondary objectives of this observational study are:

- to observe the changes in overall health status in subjects with moderate to severe plaque psoriasis treated with adalimumab for up to 12 months in routine clinical practice, by using the Short Form-36 (SF-36) questionnaire.
- to evaluate, for up to 12 months of observation, the changes in mental status in overall study population by using the Beck Depression Inventory (BDI).
- to assess the mean change in the pain score by using the Visual Analogue Scale (VAS) over 12 months of adalimumab therapy in the subgroup of patients with psoriatic arthritis identified at baseline
- to evaluate changes in occupational status in study subjects over 12 months and satisfaction related to these changes.

PROJECT TITLE: The Impact of Psychiatric Comorbidities on Quality of Life of Patients Presenting with Common Chronic Dermatological Conditions: A Saudi Arabian Perspective

RAC# 2151 146

Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Saad Alajlan, MD*

CO-INVESTIGATORS: *Haneen Salah Albarqawi, Haya Jamal Azouz*

ABSTRACT

Acne, psoriasis, dermatitis, and vitiligo are among the commonly presenting diseases in dermatology clinic. Due to their predominant presentation on the skin, many of these lesions stigmatize patients thereby compromising their self-confidence and possibly yielding anxiety, depression, and suicidal ideation. Effective management of such conditions, therefore, involves a comprehensive assessment of any possibly psychosocial comorbidity. Adequate consideration of patients' concerns does not only amend their quality of life, but it can also save their lives from impending death. This cross-sectional survey-based study aims to assess dermatologists' perspective and ways of dealing with psychosocial issues associated with commonly presenting chronic dermatological conditions. The study sample will include dermatologists from different governmental and private hospitals in Riyadh, Saudi Arabia.

INTRODUCTION

Psychosocial and psychiatric comorbidities present in 30% of dermatology clinics. Indeed, skin diseases were considered to be the fourth leading cause of nonfatal disease burden. Several prior studies addressed the psychological impact on certain dermatological conditions.

Further, several studies investigated the association of psychological comorbidities in dermatology. Dalgard et al, for instance, considered psychological comorbidities in skin diseases across 13 European countries. 12.7% of patients reported suicidal ideation while only patients presenting with psoriasis had a significant correlation. Moreover, 1 in 4 patient suffering from severe acne admitted to have suicidal thoughts. Additionally, depression was clinically apparent in 10% of psoriasis patients.

Assessing the psychological status of a patient presenting to a dermatology clinic is very crucial for providing a comprehensive treatment. The ultimate goal of any physician is to amend the quality of life of the patient. This can successfully be done with a holistic approach that takes into account all of the patient's concerns including his/her reflective thoughts of the skin condition. Dermatitis, for instance, causes consistent itching that can deprive patients from sleeping thereby causing insomnia. Other psychiatrically devastating outcome is social isolation secondary to social stigmatization due to skin condition. Hence, psychiatric comorbidities may range from mild anxiety to life-threatening suicidal attempts. Tackling every aspect of a possible psychiatric comorbidity that can detrimentally affect patients' quality of life is, therefore, indispensable.

The aim of this study is to assess dermatologists' consideration of the impact of psychiatric comorbidities on the quality of life in patients presenting with common skin conditions. The study will involve interviewing dermatologists in both governmental and private hospitals. The interview will start with open-ended questions about their individual perspectives on tackling this issue. This will be followed by a set of close-ended questions that will address several issues including the prevalence of psychiatric comorbidities in patients presenting to dermatology clinics in Riyadh, Saudi Arabia. Furthermore, few questions will address the dermatologists' consideration of specific alternative ways that have been previously mentioned in the literature including a referral to a psychiatry clinic and extensively addressing suicidal thoughts in susceptible patients. Moreover, our focus in this study is on common chronic skin condition not only because they are the most prevalent, but because they are usually not life-threatening and therefore may be over-looked.

According to Al-Hoqail, some of the commonly presenting chronic dermatology problems in Saudi Arabia include: acne, psoriasis, dermatitis, vitiligo, alopecia with the most implicated ages 21–30.

AIMS

1. To assess dermatologists' consideration of the impact of psychiatric comorbidities on the quality of life in patients presenting with common chronic skin conditions.
2. To determine the prevalence of patients presenting to dermatology clinic with psychosocial comorbidities secondary to their skin condition.
3. To provide a review of possible ways of tackling such issues in Saudi Arabia.
4. To assess local dermatologists' own ways of dealing with psychosocial issues in common skin conditions.

PROJECT TITLE: The Implementation of A Patient Assisted Mobile Teledermatology Program in Saudi Arabia Dermatologists' Perspective
RAC# 2151 145

PRINCIPAL INVESTIGATOR: *Saad Alajlan, MD*
CO-INVESTIGATORS: *Haneen Salah Albarqawi, Haya Jamal Azouz*

ABSTRACT

Teledermatology, which is the use of technology for an expanded access to patient data in order to achieve patient care over distance, has been subjected to extensive research in the past decade. Literature has reported many advantages of using teledermatology, including reduced waiting time and costs on patients. In addition to that, it was reported as a solution for the shortage of the number of dermatologists when compared to the great incidence of skin diseases. Since dermatology is primarily a visual speciality that depends on clinical and histopathological images, many studies have shown that the use of teledermatology has resulted in accurate and reliable diagnoses of a variety of skin disorders. Recently, smartphones have been increasingly accessible and affordable for the majority of patients and doctors; thus, this brought up what is called Patient-Assisted Mobile Teledermatology (PAMT), in which the patient seeks and receives medical advice directly from the dermatologist to their mobile phones. This cross-sectional survey-based study aims to measure the extent to which a "Patient-Assisted" Mobile Teledermatology program can be implemented in Saudi Arabia aiming to take dermatology care to a new level. The study sample will include dermatologists from different governmental and private hospitals in Riyadh, Saudi Arabia. The survey will be delivered by interviews, in which dermatologists will be asked about their perspective and views regarding the implementation of Patient-Assisted Mobile Teledermatology program in Saudi Arabia

INTRODUCTION

According to the American Academy of Dermatology (AAD), teledermatology has been defined as "the remote delivery of dermatologic services and clinical information using telecommunications technology". The concept of teledermatology was firstly introduced in 1995 by the dermatologists Perednia and Brown, in which they discussed the role of its implementation in helping the underserved populations in rural areas (Perednia and Brown, 1995). Several studies indicated that the use of teledermatology had an increased efficiency, thus providing an expanded access to accommodate more patients, and is a potential solution for the workforce shortage (Barbieri, et al., 2015 & Ogbechie, et al., 2015).

Adding to that, a recent study that was conducted in 2015 had reported a high feasibility and reliability of patient diagnosis using teledermatology (Nami, et al., 2015).

There are different modalities of teledermatology as classified by the American Academy of Dermatology (AAD), which are Store-and-forward and Life-interactive, which can be described as asynchronous, and synchronous methods, respectively. Furthermore, the AAD indicated that the use of teledermatology could be as direct patient-to-doctor, or doctor-to doctor consultation.

Dermatology is a specialty that is highly dependent on visual documentations for diagnoses such as clinical and histopathological images (Kanthraj, 2015). During this era, there is no doubt about the popularity and the accessibility of smartphones, which have gone beyond the limitations in image quality and screen resolution (Nami, et al., 2015). This have opened the gate for another field of teledermatology which is known as Patient-Assisted Mobile Teledermatology, in which the patient plays a dual role in seeking and receiving medical advices and consultations directly from the dermatologist to their mobile phones (Kanthraj, 2015). The patients, with the use of smartphones, can submit their medical history and images for their lesions online to a dermatologist for a direct consultation (Nami, et al., 2015). This process is illustrated in Figure 1.

Patient-Assisted Mobile Teledermatology can be classified as primary, in which the patient seeks medical consultation directly from the dermatologist, or as secondary, in which the dermatologist have the patient in their clinic for the first consultation, then they follow up their cases using teledermatology. The secondary method is known to be suitable for chronic dermatological conditions such as psoriasis and vitiligo (Kanthraj, 2015).

A study was conducted in the United States indicated that the practice pattern among dermatologists have changed, stating that younger dermatologists prefer less sessions per week and had less working hours when compared to older dermatologists (Bin Saif & Al-Haddab, 2010). This indicates the need of suitable solutions to meet the population's demand and to achieve better dermatology care. It is stated that the use of Mobile Teledermatology has shown a great diagnostic concordance with face-to-face consultation (Kaliyadan, et al., 2013).

The current status of dermatology in Saudi Arabia is unbalanced in several ways. In 2007, there were only 901 dermatologist in Saudi Arabia with an estimated population of 23 million (Bin Saif & Al-Haddab, 2010), however no more recent statistics were provided. Furthermore, some areas of Saudi Arabia are oversupplied by dermatologists, while other areas are undersupplied (Bin Saif & Al-Haddab, 2010). Implementing a Patient-Assisted Mobile Teledermatology program can help in solving these issues in Saudi Arabia, as it meets the demands of this time. There was only one previous study that was conducted in Saudi Arabia regarding the use of Mobile Teledermatology, as it measured patients'

satisfaction toward this service. The majority of the patients were comfortable with having their body parts photographed for a teledermatology consultation, and they reported that they are satisfied with it (Kaliyadan, et al., 2013).

This study aims to examine the idea of implementing a Patient-Assisted Mobile Teledermatology program in Saudi Arabia from dermatologists' perspective. This study will investigate if the dermatologists used or are willing to use such a service in the future, and what are the benefits and the barriers from implementing this idea. Further, the study will examine if a Patient-Assisted Mobile Teledermatology program is applicable in Saudi Arabia due to some cultural and religious factors in order to design a Patient-Assisted Mobile Teledermatology program that meets the demand of the country.

AIMS

The study mainly aims to investigate dermatologists' perspective about implementing a Patient-Assisted Mobile Teledermatology program in Saudi Arabia, which will help in improving the status of dermatology care to meet the population's demands. Adding to that, the study will provide us with some benefits, uncover obstacles, and suggest possible ways in order to measure the extent of which a Patient-Assisted Mobile Teledermatology program can be implemented in a context that will suit Saudi Arabia.

PUBLICATIONS

- *RAC # 2150 290:* Alajlan S, Alaqeel AM, Alfurayh NA, Alhedyani AA. Sirolimus for Treatment of Kaposiform Hemangioendothelioma Associated with Kasabach-merritt Phenomenon.
- *RAC # 2150-286:* Alajlan S, Azouz H, Albarqawi H, Badran M. Remarkable Reduction of Cystic Hygroma in a Young Infant through the Combined Administration of Sirolimus and Sclerotherapy: A Case Report and a Review of Literature. Presented in the Surgical Research Day 21st International Workshop of the International Society of the Study of Vascular Anomalies. *Journal of American Academy of Dermatology*.

FAMILY MEDICINE & POLYCLINICS

FAMILY MEDICINE & POLYCLINICS

CHAIRMAN
Abdullah Alkhenizan, MD

Department Research Committee

CHAIR
Aneela Hussain, MD

MEMBERS
Hussam Jnaid, MD
Patricia McWalter, MD
Nusrat Qazi, MD

THE REPORT HIGHLIGHTS RESEARCH AND SCHOLARLY ACTIVITIES by our department members. Although the department has a relative modest number of faculty members with protected time for research, the collaborative culture within the department has led a number of publications.

The Department of Family Medicine & Polyclinics is active in enriching the research activities of the department through its Department Research Committee. The function of this Committee is to provide academic and administrative support to physicians in the preparation and submission of their proposed research projects and to give assistance to investigators in a manner consistent with approved policies and procedures of KFSH&RC. As a result, the number of research projects, publications, abstracts and international presentations has increased compared to previous years. The Committee is comprised of four physicians and one research coordinator.

RAC APPROVED RESEARCH PROJECTS FOR 2015

PROJECT TITLE: A Survey of Flu Vaccine Use and Effectiveness in KFSH&RC
RAC #2151 028

PRINCIPAL INVESTIGATOR: *Ibtesam Saleh, MD and Abdelghafour Al Omari, MD*
CO-INVESTIGATORS: *Abdullah Alkhenizan, MD and Aneela Hussain, MD*

OVERVIEW/AIMS

a. To determine the percentage of patients who come with flu symptoms whether or not they had influenza vaccine earlier and the frequency of seriousness of their symptoms
b. To determine the percentage of all the patients who used the flu vaccine and get sick with influenza virus
c. To offer insight information about compliance to take the flu vaccine and the effectiveness of the flu vaccine in protection of influenza viruses indifferent age group and disease

PROJECT TITLE: The Relationship Between 25 (OH) D Levels (Vitamin D) and Bone Mineral Density (BMD) in a Saudi Population in a Hospital-Based Setting
(RAC #2151 125)

PRINCIPAL INVESTIGATOR: *Abdullah Alkhenizan, MD*
CO-INVESTIGATORS: *Ahmed Mahmoud, MD, Aneela Hussain, MD, Suad Alsoghayer*

OVERVIEW/AIM: To investigate the correlation between bone mineral density (BMD) and vitamin D levels among patients in primary care clinics.

PROJECT TITLE: SYMATONA
RAC #2151 015

PRINCIPAL INVESTIGATOR: *Abdullah Alkhenizan, MD*
CO-INVESTIGATORS: *Aneela Hussain, MD, Mohammed Shafiq, MD*

OVERVIEW/AIM: To establish "SYMATONA" a biobank which contains phenotypic and genotypic data, within the Center for Peronalized Medicine, at the King Faisal Specialist Hospital & Research Centre.

PROJECT TITLE: SYGMIA2 Trial: A 52-week, Double-blind, Randomized, Multi-centre, Phase III, Parallel-group Study in Patients 12 Years and Older with Asthma: Evaluating the Efficacy and Safety of Symbicort (Budesonide/Formoterol) Turbuhaler
RAC #2151 001

PRINCIPAL INVESTIGATOR: *Hussam Jnaid, MD*
CO-INVESTIGATORS: *Abdullah Alkhenizan, MD, Abdulwahab Heggi, MD, Mohammed Alswes, MD, Kassay El Abd, MD, Mohammed Albaqami*

OVERVIEW/AIM:

a. To demonstrate that Symbicort Turbuhaler 160/4.5 µg 'as needed' is superior to Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'
b. To estimate the difference in efficacy between Symbicort Turbuhaler 160/4.5 µg 'as needed' and Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'

PLANNED RESEARCH PROJECTS FOR 2015

PROJECT TITLE: The Effect of SSRIs on Diabetic Patients Who have Been Diagnosed with Depression and Anxiety

PRINCIPAL INVESTIGATOR: *Mohammed Alswes, MD*
CO-INVESTIGATOR: *Suad Alsoghayer*

PROJECT TITLE: Presence of Cardiovascular Risk Factors Among Patients of a Primary Care Setting

PRINCIPAL INVESTIGATOR: *Abdullah Alkhenizan, MD and Aneela Hussain, MD*
CO-INVESTIGATOR: *Suad Alsoghayer*

SELECTED ACHIEVEMENTS FOR 2015

a. Twenty-two (22) research projects have been approved by RAC approved since we intensified our Department Research Committee in 2010.
b. Three (3) original research projects were accepted for publication in 2015, awaiting confirmation of the date for publication:
   - Predictive factors and clinical biomarkers for treatment in patients with chronic pain due to osteoarthritis with a central sensitization component (submitted to Int J of Clinical Practice)
     Author: Akinci, Aysen
     Co-authors: Shaker, Mohammed; Chang, Ming Hong; Cheung, Chi Woi; Danilon, Andrey
   - Attitudes and Perception Towards HPV Vaccination Among Young Women in Saudi Arabia (submitted to Journal of Family and Community Medicine)
     Author: Aneela Hussain, MD
     Co-authors: Nusrat Qazi, MD; Amal Alshmassi, MD; Patricia McWalter, MD; Ahmed Abdulkarim, MD; Samina Farooqi, MD; Abdullah Alkhenizan, MD
   - Sociodemographic characteristics and sexual behavior as risk factors for human papillomavirus infection in Saudi Arabia" (submitted to International Journal of Infectious Diseases)
     Author: Mohammed Al-Ahdal
     Co-Authors: Fatimah S. Alhamlan, Ph.D.,; Hadeel Khayat; Susie Ramisetty-Mikler, Tarfah Al-Muammar, Asma Tulbah, Ismail Al-Badawi, Wesam Kurdi, Maha Tulbah, Abdullah Alkhenizan, Aneela Hussain, Marium Ahmad

PUBLICATIONS

- S Al Othman, A Haoudi, S Alhomoud, A Alkhenizan, T Khoja, A Al Zahrani. Tackling Cancer Control in the Gulf Cooperation Council Countries. *Lancet International,* May 2015.
- Muammar T, McWalter P, Alkhenizan A, Shoukri M, Gabr A, Bin AA. Management of Vaginal Penetration Phobia in Arab Women: A Retrospective Study. *Ann Saudi Med*. 2015 Mar-Apr;35(2):120-6. doi: 10.5144/0256-4947.2015.120.
- Muneerah Albugami, Yasmin Al Twaijri, Hussam Jnaid, Abdulwahab Heggi, Abdelazeim Elamin, Rania Abdelreheem, Siddiquee Mohammed, Walae Alahmadi, Noura Alturaif. Health Care Maintenance of Saudi Elderly Women in Outpatient Clinics. *American Journal of Internal Medicine*, 2015; 3(5): 197-203. Published online August 11, 2015 (http://www.sciencepublishinggroup. com/j/ajim); doi: 10.11648/j.ajim.20150305.11; ISSN: 2330-4316 (Print); ISSN: 2330-4324 (Online).
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- T. Muammar, P.McWalter/M. Shoukri. Experience of Treating Vaginismus in Saudi Population. *Annals of Saudi Medicine*, Dec, 2014.

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- A Hussain, B Cunha, et al. Smallpox. Infectious Diseases book. *Medscape*, Dec 2013.
- P Ellsworth, A Hussain, et al. Overactive Bladder. Urology Book. *Medscape*, Aug 2013 (peer reviewed)
- F Hussain, Hussain A et al. Gynecologic Tumor Markers. Obstetrics & Gynecology book. *Medscape*, August 2012.
- Alkhenizan A, Shaw C. The attitude of health care professionals towards accreditation: A systematic review of the literature. *J Family Community Med*. 2012 May; 19(2):74-80.
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HEART CENTRE

HEART CENTRE

DIRECTOR

Jehad Al Buraiki, MD

THE HEART CENTRE IS COMMITTED TO EXCELLENCE IN PATIENT CARE, teaching, and research. Its mandate includes research on the challenges of cardiovascular diseases facing the people of Saudi Arabia and its objective is to increase scientific knowledge of cardiovascular diseases, including their epidemiology, risk and risk factors, prevention, detection and diagnosis, treatment and prognosis, and to initiate cardiovascular, evidence-based programs.

In 2015 the Heart Centre had 69 approved/ongoing research projects. These projects included prospective studies, retrospective records review and analysis, registries, interventional, diagnostic research, and basic research. Heart Centre has 56 Retrospective and 13 Prospective studies, out of these 6 are sponsored, 3 grand funded studies and two KACST's projects. All sections of the Heart Centre have research proposals as follows: Adult Cardiology=26, Adult Cardiovascular Surgery=15, Pediatric Cardiology=16, Pediatric Cardiovascular Surgery=5, Adult and Pediatric Cardiovascular Surgery (combined)=06, Adult and Pediatric Cardiology (combined)=1. Fifteen (15) of these projects were completed in 2015. Also for 2015, the Heart Centre submitted 25 Publications and 34 Abstract & Oral presentations.

The Heart Centre continues to develop its Strategic Research Plan (SRP) which is designed to develop and sustain significant, internationally acknowledged research in several thematic areas relevant to the high incidence of cardiovascular diseases in the Kingdom. The Heart Centre plans to significantly increase its research capacity in each of these areas and to become recognized internationally for its high caliber research.

PROJECT TITLE: Congenital Heart Disease Registry
RAC#: 991026

PRINCIPAL INVESTIGATORS: *Mansour Al Joufan, MD / Zohair Al-Halees, MD*

PROJECT DESCRIPTION: This Registry is a collaborative project between the Heart Centre and the Biostatistics, Epidemiology and Scientific Computing Department, Research Centre. It collects data on pediatric patients with congenital heart disease and publishes an annual report.

PROGRESS: This Registry is on-going. The cumulative number of subjects enrolled is 24844. The number of subjects enrolled during the last approval year is 694.

PROJECT TITLE: RIVER Registry-RIVaroxaban Evaluation in Real life setting
RAC#: 2151127

PRINCIPAL INVESTIGATORS: *Bandar Al Ghamdi, MD*

PROJECT DESCRIPTION: Prospective, multicentre, international Registry of male and female patients newly diagnosed with Atrial Fibrillation and treated with Rivaroxaban.

Registry Objectives:

- To assess the rate of stroke and systemic embolisation in Registry participants.
- To assess patient outcomes with specific reference to:
  - The incidence of bleeding complications
  - Therapy persistence (including discontinuation, interruption and changes of therapy regimen)

PROGRESS: Ongoing. Enrolled 3 patients in the study.

PROJECT TITLE: Should We Treat Aortic Valve Pathology As An Aortic Root Disease? 15-Years Follow-up With Different Approaches
RAC#: 2151085

PRINCIPAL INVESTIGATORS: *Feras Khaliel, MD*

PROJECT DESCRIPTION: This is a retrospective study; the medical records of all the patients with aortic stenosis or aortic root dilatation between the ages of 20 to 50 years who underwent isolated aortic valve replacement (with mechanical or bioprosthetic valve), Aortic Valve Repair, Ross procedure or Bentall procedure from 1st January 1995 to 31st December 2014 will be reviewed.

The aims of this study are:

1. To determine the outcomes of the patients with aortic stenosis regardless of presence or absence of aortic root dilatation who underwent isolated aortic valve replacement, Ross procedure or Bentall procedure, in a young population between the ages of 20 to 50 years at KFSH&RC.
2. To compare the outcomes with reported outcomes at other centers.

PROGRESS: Onging. Started enrolling the patients.

PROJECT TITLE: Pediatric Heart Catheterization Registry
RAC#: 2001053

PRINCIPAL INVESTIGATORS: *Fadel Al Fadley, MD*

PROJECT DESCRIPTION: The aim of this project is to establish a registry for all diagnostic and interventional pediatric cardiac catheterizations performed at the KFSH&RC.

PROGRESS: This is an ongoing Registry. The cumulative number of subjects enrolled is 5292. The number of subjects enrolled during the last approval year is 402.

PROJECT TITLE: How to Approach Familial Dyslipidemia? PCI Versus CABG Surgery
RAC#: 2141106

PRINCIPAL INVESTIGATORS: *Feras Khaliel, MD*

PROJECT DESCRIPTION:

1. To Evaluate the patency of coronary bypass grafts, and observe the efficacy of the anti-cholesterol treatments
2. To Evaluate the patency of the percutaneous coronary intervention (PCI) on these patients, and observe the rate of restenosis
3. To evaluate the rate and prognosis of LT post CABG and / or PCI
4. To be able to identify the best intervention to be given for those group of patients.
5. To compare the outcomes with reported outcomes at other centers.

PROGRESS: Ongoing. Started screening the hyperlipidemia patients with coronary artery surgery, post CABG, post PCI, and liver transplants in post CABG.

PROJECT TITLE: Valve Registry
RAC#: 2001055

PRINCIPAL INVESTIGATORS: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: This Registry includes data on KFSH&RC patients (both adult and pediatric) who underwent valve surgery. Data on these patients' pre-operative, peri-operative, post-operative and follow-up course, including data on events such as thromboembolism, endocarditis, rhythm variations, anticoagulation, anticoagulation-related bleeding, readmissions, re-operations, symptomology and medications has been collected.

PROGRESS: This is an ongoing Registry. The cumulative number of subjects enrolled is 8776. The number of subjects enrolled during the last approval year is 302.

PROJECT TITLE: Coronary Artery Calcium Score in a High Risk Asymptomatic Women in Saudi Arabia
RAC#: 2151158

PRINCIPAL INVESTIGATORS: *Jehad Al Buraiki, MD, Ahmed Fathala, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective, observational study. The aim of this study is to investigate the prevalence and percentiles of CAC score in high risk asymptotic women in Saudi Arabia with comparison of age specific CAC percentiles derived from large population based published study in USA.

PROGRESS: Ongoing.

PROJECT TITLE: How Aware Are Patients Of Their Rights; A Multi-Centric Middle-Eastern Study
RAC#: 2151152

PRINCIPAL INVESTIGATORS: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: This is a cross-sectional; multicentric study. After determination of the statistically significant number of patients required for this study, patients are going to be chosen at random from three big centers in Riyadh, Saudi Arabia; including King Faisal Specialist Hospital & Research Centre, King Fahad Medical City & Security Forces Hospital.

The aims of this study are:

1. To determine the level of awareness in our patients of their rights.
2. To assess reasons if the levels are below standards.
3. To suggest ways to improve the proper implementation of the patients' bill of rights.

PROGRESS: Ongoing. Started enrolling the patients.

PROJECT TITLE: Percutaneous Trans Luminal Coronary Angioplasty (PTCA) Registry
RAC#: 2001057

PRINCIPAL INVESTIGATORS: *Hani Al Sergani, MD*

PROJECT DESCRIPTION: This is an on-going Registry of patients who underwent Percutaneous Trans- luminal Coronary Angioplasty (PTCA) at the KFSH&RC. The objective is to examine revascularization strategies for coronary artery disease and the outcomes of interventions for patients with acute coronary syndrome and chronic coronary insufficiency.

PROGRESS: This Registry closed in December 2015. The cumulative number of subjects enrolled is 4123. The number of subjects enrolled during the last approval year is 143.

PROJECT TITLE: KFHI Surgery Registry
RAC#: 2001058

PRINCIPAL INVESTIGATORS: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: This Registry includes all cardiovascular surgical procedures performed at the KFSH&RC and is utilized as a valuable research and program administrative tool.

PROGRESS: This is an on-going Registry. The cumulative number of subjects enrolled during the lifetime of the Project is 35102. The number of subjects enrolled during the last approval year is 1257.

PROJECT TITLE: Is Myomectomy Justifiable in Preventing Recurrence of Discrete Sub aortic Obstruction?
RAC#: 2031072

PRINCIPAL INVESTIGATORS: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: This is a retrospective study of patients with atrioventricular valve regurgitation who underwent a modified Fontan operation at the KFSH&RC. The aim of the Study is to compare the recurrence of sub aortic obstruction in patients with or without of myomectomy for discrete sub aortic stenosis.

PROGRESS: Ongoing with long term follow up. 156 patients have been enrolled. Now in a process of fourth review and re-validating of the data. Waiting for the statistical analysis.

PROJECT TITLE: Fontan operation early and late results: A 20 years single center experience
RAC#: 2151005

PRINCIPAL INVESTIGATORS: *Abdullah AL-Sehly, MD*

PROJECT DESCRIPTION: Retrospective review of all patients (children and adults) underwent Fontan procedure at KFSH&RC, Riyadh, Saudi Arabia over past 20 years. We want to look for the short and long-term results and sequelae associated with Fontan palliation.

To conduct a detailed analysis of actuarial long-term survival, modes of death, and predictors of morbidity and mortality in patients with diverse

forms of Fontan palliation from tertiary cardiac care center over 20 years period. Study the preoperative, operative, and postoperative clinical and hemodynamic data.

PROGRESS: Ongoing.

PROJECT TITLE: Electrocardiogram Screening for School Children: A Cross- Sectional, Population Based Study
RAC#: 2101092

PRINCIPAL INVESTIGATORS: *Majid Al Fayyadh, MD*

PROJECT DESCRIPTION: The objective of this study is to assess whether an ECG performed during childhood may contribute to the early identification of subjects at risk for cardiovascular morbidity and mortality, particularly disease whose prognosis may be significantly improved by an adequate therapy. Additionally, the prevalence, the clinical significance and the characterization of ECG abnormalities will be determined in a large population of children.

PROGRESS: Ongoing. Totally 14483 subjects have been enrolled in the study. No subjects enrolled during the last approval year. KFSH&RC physicians Completed the reading of all ECG's. Abnormal ECG's assessed and sends back to the center to repeat the ECG. ECG's repeated for 404 children. Comprehensive cardiac evaluation is being done for students with border line and abnormal ECG screening. Study completed successfully and Final report approved in August 2015.

PROJECT TITLE: Long-Term Outcome of Mitral Valve Repair Versus Mitral Valve Replacement Using Mechanical and Bio prosthetic Valves
RAC#: 2051016

PRINCIPAL INVESTIGATORS: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: This retrospective review is studying the long-term effect of mitral valve repairs versus mitral valve replacement using mechanical and/or bio prosthetic valves.

The aims of the Study are to:

1. Compare the event-free survival periods associated with mitral valve repairs and replacement.
2. Describe the incidences of redo repairs and redo replacements.
3. Identify the factors contributing to the need for redo surgeries, and
4. Study the above factors on mortality and morbidity.

PROGRESS: The data has been cleaned and validated on approximately 779 patients who meet the Study criteria. Second follow-up data collection completed and statistical analysis done. Wating to finalize the report.

PROJECT TITLE: PREMIER (Pulmonic Valve Replacement Multi-Discipline Emea Registry)
RAC#: 2111043

PRINCIPAL INVESTIGATORS: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: This is an international, multi-center, prospective, consecutively enrolled, observational registry. The purpose of this registry is to expand upon existing data sets, to identify patient characteristics and indicators related to complications and clinical benefits for symptomatic patients with a regurgitant or stenotic pulmonary valved conduit undergoing treatment with the commercially available Edwards SAPIEN XT™ Valve, and delivery devices.

PROGRESS: Ongoing. 18 patients have been enrolled. 5 years follow up ongoing according to the protocol.

PROJECT TITLE: Gulf implantable Cardioverter Defibrillator study (Gulf ICD)
RAC#: 2131159

PRINCIPAL INVESTIGATORS: *Bandar Al Ghamdi, MD*

PROJECT DESCRIPTION: This is a prospective observational multi-center multi-national study of the characteristics and outcomes of patients receiving implantable cardioverter-defibrillators (ICD) in the Arab Gulf region. A total of 1, 000 patients will be enrolled. Data on baseline clinical characteristics, ICD programming parameters, inpatient outcomes, and clinical events such as mortality and ICD discharges over 1 year of follow-up will be collected.

The primary objective of the study is to describe the characteristics and outcomes of patients receiving implantable cardioverter-defibrillators (ICD) in the Arab Gulf region. Once completed, the data collected from Gulf ICD will be available for further secondary analyses including a description of ICD implant indications and programming patterns in the Gulf.

PROGRESS: Enrolled 75 patients in the study as per the study protocol. 25 patients enrolled in the last approval year. Continuing the 6 months follow up.

PROJECT TITLE: Detection of increased pulmonary vascular resistance by echocardiography in patients with left heart disease: Effect of optimized medical treatment
RAC#: 2141004

PRINCIPAL INVESTIGATORS: *Nedim Selimovic, MD, PhD*

PROJECT DESCRIPTION: To investigate the short-term dynamic changes in PVR assessed by the new method following optimization of heart failure treatment.

PROGRESS: Study closed in October 2015, due to lack of personnel.

PROJECT TITLE: THEMIS STUDY (Effect of Ticagrelor on Health outcomes in Diabetes Mellitus Patients Intervention Study)
RAC#: 2141099

PRINCIPAL INVESTIGATORS: *Rasha Bazari, MD*

PROJECT DESCRIPTION: THEMIS STUDY is a Multinational, Prospective, Randomised, Double blind, Placebo-Controlled Trial to evaluate the effect of Tricagrelor 90mg twice daily on the incidence of cardiovascular death, myocardial infarction or stroke in patients with type 2 diabetes mellitus. To compare the effect of long-term treatment with ticagrelor 90 mg twice daily (bd) vs. placebo for the prevention of major cardiovascular (CV) events (composite of CV death, myocardial infarction [MI] or stroke) in patients with Type 2 Diabetes Mellitus (T2DM) at high risk of CV events, but without a medical history of previous MI or stroke.

PROGRESS: One patient enrolled in the study according to the protocol. Doing screening for all the adult cardiology clinic patients.

PROJECT TITLE: Bone Density in Heart Transplanted Patients In Kingdom Of Saudi Arabia
RAC#: 2141095

PRINCIPAL INVESTIGATORS: *Nedim Selimovic, MD, PhD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective, observational study. Medical files

of all consecutive heart transplanted patients since the beginning of 2009 until August 2013 will be reviewed.

The purposes of this study are:

1. To determine incidence of osteopenia/ steoporosis in heart transplantation candidates and heart transplanted patients 1 and 2 year after HTx.
2. To evaluate association between demographic characteristics (age, gender, BMI) and development of osteoporosis
3. To characterize potential influence of vitamin D deficiency, thyroid function and renal function on more rapid development of bone loss.
4. To evaluate long-term use of corticosteroids and calcineurin inhibitors (cyclosporine, tacrolimus) and associated bone loss.
5. To measure changes in bone mineral density pre-transplant and 1 and 2 year after transplantation.
6. To identify any differences in BMD between lumbar spine and femoral neck pre-transplant and 1- and 2 year follow-up
7. To identify possible differences in grade of osteoporosis between different gender (women vs. men) and differences between postmenopausal women and childbearing women.

PROGRESS: Enrolled 63 patients in the study. Statistical analysis done and final report submitted in September 2015. Study abstract presented in Saudi Heart Symposium 2015.

PROJECT TITLE: Genetics of Mandelian Cardiovascular Disorders in Saudi Arabia
RAC#: 2080032

PRINCIPAL INVESTIGATORS: *Majid Al Fayyadh, MD/Zuhair Al-Hassnan, MD*

PROJECT DESCRIPTION: The aim of this research is to identify genes responsible for Mendelian Cardiovascular Disorders (MCD) in the Saudi population. This will provide molecular characterization of patients with known syndromes as well as those with novel non-described phenotypes. The identification of the underlying genes will provide major practical information.

PROGRESS: Ongoing. During the lifetime of the project, we have recruited 677 patients and family members with various forms of Mendelian cardiovascular disorders. Current report enrolled 164 patients. In a consanguineous family with Hypertrophic cardiomyopathy (HCM) in 4 children, homozygosity and whole exome sequencing identified a potential novel locus on chromosome 3. In a family with fatal form of cardiomyopathy, a novel mutation was detected in AGK gene.

PROJECT TITLE: Discovery of Genetic Causes for Human Congenital Malformations
RAC#: 2091038

PRINCIPAL INVESTIGATORS: *Majid Al Fayyadh, MD*

PROJECT DESCRIPTION: To enrich the potential discovery of mutant alleles (especially recessive ones) causing congenital cardiovascular malformations (CCM), the aim of this research is to study these birth defects in Saudi Arabia. This collaborative work brings together human molecular geneticists and clinicians to discover genetic causes of CCM.

PROGRESS: Ongoing. Recruited 463 patients and family members. Current report enrolled 67 patients. We will continue patient enrollment and

patient follow-up on the enrolled subjects as per study protocol.

PROJECT TITLE: Acute Angulation of the Aortic Arch Late After the Arterial Switch Operation for Transposition of the Great Arteries: Impact on Blood Pressure and Cardiac Mechanics
RAC#: 2141092

PRINCIPAL INVESTIGATORS: *Di Salvo Giovanni, MD*

PROJECT DESCRIPTION: This is a retrospective study. The clinical and the standard echocardiographic data (From 1st January 2006 to 31st July 2014) of patients who underwent arterial switch operation for simple d-transposition of the great arteries (d-TGA) will be reviewed. In addition on digitally stored echo-images additional analysis to assess left ventricular deformation will be performed by using a dedicated software. According to standard echo data patients will be divided in two groups: Acute aortic arch angulation (AAAA-Group) and non- AAAA group.

The aims of this study are:

1. To assess the occurrence of aortic arch acute angulation (AAAA) in patients after successful ASO
2. To assess the impact of AAAA on cardiac morphology and function in patients after successful ASO using standard echocardiography and
3. To assess cardiac function using bi-dimensional strain imaging in patients after successful ASO and its relationship with AAAA.

PROGRESS: Enrolled 75 patients in the study. Statistical analysis done and final report submitted on October 2015. To the best of our knowledge this is the largest study on ASO patients by using STE. We demonstrated that in asymptomatic ASO patients despite a normal LV EF there is a significant reduction in longitudinal myocardial deformation significantly correlated with the age at surgical repair. Thus our findings suggest early

operations for d-TGA patients and to continue monitoring ventricular function in such patients assessing also global longitudinal deformation.

PROJECT TITLE: Clinical & Molecular Characterization of Patients With Inherited Arrhythmogenic Disorders
RAC#: 2050035

PRINCIPAL INVESTIGATORS: *Majid Al Fayyadh, MD*

PROJECT DESCRIPTION: This is a prospective study to identify genes responsible for inherited arrhythmogenic disorders in the Saudi population. Detecting the causative mutations in affected families will serve several clinical purposes including enabling clinicians to confirm the diagnosis, stratify patients, and apply prophylactic measures. Due to the fact that inherited arrhythmogenic disorders are characterized by incomplete penetrance, the most important contribution of mutation detection to patient management is the identification of asymptomatic carriers and hence, implementing prophylactic management.

PROGRESS: Ongoing. Recruited 688 patients and family members in life time and last progress report time 148 patients & families.

PROJECT TITLE: Tetralogy of fallot (TOF): A retrospective Chart Review
RAC#: 2031061

PRINCIPAL INVESTIGATORS: *Saud Al Oufi, MD*

PROJECT DESCRIPTION: This is a Retrospective chart review. Study completed in 2009 and PI decided to re-open the study.

The purpose of this study was to review of Tetralogy of Fallot patients in KFSH&RC/KFHI and to study their progress through clinical follow-up and Echocardiography visits. Reactivate this study to further follow up of previous patients and enroll new patients who had TOF repair from 2/7/2009 to 31/3/2015. This will provide a longer follow-up and increased number for a more robust publication in the future.

PROGRESS: Ongoing. Screened about 500 patients and data collection started.

PROJECT TITLE: Heart Centre Registry for the Long Term Outcome of Aortic Valve Replacement Using the Ross Procedure
RAC#: 2051055

PRINCIPAL INVESTIGATORS: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: A Valve Registry exists that was discontinued January 5, 2008. In this new Registry, we will go back and include that data retrospectively and add the additional data up to December 31, 2014. Our aims to evaluate our experience and the long-term outcome of aortic valve patients requiring surgical intervention through Ross Procedure through:

1. Retrospective review of our Valve Registry Database
2. Ongoing prospective enrollment of subjects needing Aortic Valve Replacement
3. Measure short and long term outcomes for patients with aortic valve problems requiring surgery.

PROGRESS: Study re-opened on July 2015. Enrollment started and data collection in progress.

PROJECT TITLE: Detection Of Increased Pulmonary Vascular Resistance By Echocardiography In Patients With Left Heart Disease: A Prospective, Non-Randomized Study
RAC#: 2121097

PRINCIPAL INVESTIGATORS: *Nedim Selimovic, MD, PhD*

PROJECT DESCRIPTION: This is a prospective study to estimate the pressure in the heart chambers using echocardiography. This study will look at a new echocardiography method to identify patients with increased resistance to flow in the pulmonary circulation.

PROGRESS: Enrolled thirty-nine (39) patients in the study. Due to lack of personnel study closed in October 2015.

PROJECT TITLE: Comparing the Assessment of the Aortic Annulus Diameter Before Trans Catheter Aortic Valve Implantation (TAVI) With Echocardiography Versus With Cardiac CT
RAC#: 2121106

PRINCIPAL INVESTIGATORS: *Jehad Buraiki, MD*

PROJECT DESCRIPTION: This is a retrospective to compare annulus measurement with multislice computed tomography (MSCT), 2D transthoracic echocardiography and transesophageal echocardiography and to study the immediate effects of successful TAVI on the left ventricular dimensions, systolic function and diastolic function by ECHO.

PROGRESS: Enrolled twenty nine (29) patients in the study. Statistical analysis done. Final report submitted on March 2015.

PROJECT TITLE: Single Center Experience with Trans-apical & Trans-Femoral Sapien® Aortic Valve Implantation
RAC#: 2121113

PRINCIPAL INVESTIGATORS: *Feras Khaliel, MD*

PROJECT DESCRIPTION: This is a retrospective study to assess the outcomes of the high risk patient post-trans apical aortic valve implantation (TAVI) and the results of the octogenarians post trans apical aortic valve implantation. Results (mortality and morbidity) of the trans apical to the trans femoral approach will be assessed and compared with international data.

PROGRESS: Ongoing; Extended the study period for 2 more years and enrolled 68 patients total. 16 patients have been enrolled during the last progress report approval period.

PROJECT TITLE: Outcomes of Trans Catheter Versus Surgical Closure of Secondum Atrial Septal Defect in Children and Adults at KFSH&RC
RAC#: 2121115

PRINCIPAL INVESTIGATORS: *Amal Silmi, MD*

PROJECT DESCRIPTION: This is a retrospective study to determine the outcomes (efficacy, success, and safety) in patient who underwent trans catheter device closure of secondum atrial septal defect from 1998 to 2008.

PROGRESS: Ongoing, 536 patients were enrolled. 154 patients have been enrolled during the last progress report approval period. P I left the institution and Co PI taken over the study.

PROJECT TITLE: Risk Factors and Outcome of Non-Infected Masses attached to Cardiovascular Implantable Electronic Devices (CIED) Leads
RAC#: 2151025

PRINCIPAL INVESTIGATORS: *Shafquat Azam, MD*

PROJECT DESCRIPTION: This will be a retrospective case control study. The medical records of consecutive patients who have CIED lead identified on echocardiogram will be reviewed from 1st January 2000 to 31st December 2014.

The aims of this study are:

1. To determine risk factors that contribute to development of thrombus on CIED lead
2. To determine complications of thrombus formation on CIED lead
3. To determine response of thrombus on CIED lead to treatment.

PROGRESS: Enrolled 25 patients in the study. Abstract submitted to 2016 Heart Rhythm, 37th Annual Scientific Sessions.

PROJECT TITLE: Assessment of Beta Blockers Effect on Hearing Function in Cardiac Patients at the KFSH&RC Heart Centre – a Cross Sectional Study
RAC#: 2121131

PRINCIPAL INVESTIGATORS: *Bandar Al Ghamdi, MD*

PROJECT DESCRIPTION: This is a non-randomized, cross sectional study in patients to measure hearing loss of patients receiving β-blockers and compare the hearing loss in patients who receive β-blockers with patients who do not receive β-blockers.

PROGRESS: Enrolled 258 patients in the study. 126 patients match the criteria and had the hearing test. 87 patients excluded from the study due to various reasons. Statistical analysis done and preparing for the Final report.

PROJECT TITLE: To Assess the Long Term Outcome of Surgical Rheumatic Tricuspid Valve (TV) Repair and Comparison with Tricuspid Valve Replacement.
RAC#: 2121136

PRINCIPAL INVESTIGATORS: *Feras Khaliel, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective study to determine the prevalence of significant primary rheumatic TV, study the intermediate-term outcome of patients undergoing TV repair for significant TR, and compare the difference in intermediate-term outcome between patients undergoing TV repair vs. TV replacement.

PROGRESS: Ongoing; 73 patients have been enrolled. 56 patients during the last progress report period. Preliminary statistical analysis done. However needed a higher sample size to achieve the significance. Continuing patient enrollment.

PROJECT TITLE: AdaptResponse Study
RAC#: 2151026

PRINCIPAL INVESTIGATORS: *Shafquat Azam, MD*

PROJECT DESCRIPTION: This is a prospective, randomized, controlled, interventional, single-blinded, multi-center, post-market, global Cardiac Resynchronization Therapy (CRT) in heart failure (HF) clinical study.

The purpose of this clinical study is to test the hypothesis that CRT devices which contain the AdaptivCRT (aCRT) algorithm have a superior outcome compared to standard CRT devices in CRT indicated patients with normal atrio-ventricular (AV) conduction and left bundle branch block (LBBB).

PROGRESS: Ongoing. Enrolled one patient in the study as per the protocol.

PROJECT TITLE: Surgical Outcomes And Quality Of Life In Multiple Sternotomies Post Cardiac Surgery: Experience At Heart Centre
RAC#: 2151024

PRINCIPAL INVESTIGATORS: *Feras Khaliel, MD*

PROJECT DESCRIPTION: This is a retrospective study. The medical records of cardiac surgery patients aged 14 and above who underwent redo valvular surgeries (including mitral, aortic, tricuspid, and pulmonary) valve replacement surgery from 01 January 2003 to 31 December 2014 will be reviewed.

The aims of this study are:

1. To determine the surgical outcomes in patients who underwent multiple sternotomies.
2. To identify risk factors associated with redo surgery and their implication.

PROGRESS: Ongoing. Started enrolling the patients.

PROJECT TITLE: The Incidence, Risk Factors & Prognostic Implications of Acute Cardio Renal Syndrome; A Retrospective Analysis at the Heart Centre
RAC#: 2121040

PRINCIPAL INVESTIGATORS: *Bandar Al Ghamdi, MD*

PROJECT DESCRIPTION: This is a non-randomized retrospective study to determine the incidence and risk factors of the CRS type 1 patient at the Heart Centre.

PROGRESS: Enrolled 123 patients in the study and 68 patients in the current year. Statistical analysis done and final report submitted on June 2015. Cardio Renal Syndrome type 1 patient's form around 17% of our patient population admitted with heart failure at our tertiary care hospital. These patients

have a much more severe in-hospital course; a higher mortality and a higher re-hospitalization rate, when compared with their counterpart population. This reflects into the significance of the inter-connection between the two major organs, and implies that the heart-kidney interface works collectively to further accelerate injury and dysfunction in heart failure patients.

PROJECT TITLE: Quadripolar Leads for the Management of Heart Failure Patients in the Middle East (QUADRA ME)
RAC#: 2141074

PRINCIPAL INVESTIGATORS: *Bandar Al Ghamdi, MD*

PROJECT DESCRIPTION: This is a prospective, randomized, multicenter study. We are aiming for 175 patients in each arm (350 overall). All participants must be implanted with a St Jude Medical (SJM) CRT-D device and SJM Quadripolar lead system. Patients who fulfill the criteria for CRT D implant, will be invited to participate in this clinical investigation. Patients implanted with chronic leads requiring device upgrade to CRT-D can also be enrolled in the study, provided they are receiving a CRT-D device for the first time. Patients are followed up for 6 months post implant.

The objective of this study is to compare the clinical response of two different left ventricular pacing optimization modalities in a CRT patient population with LV Quadripolar leads. These are empirical (anatomical) and electrical according to the device RV-LV Conduction Time, using the Vect Select feature.

PROGRESS: Ongoing. Enrolled 5 patient's in the study as per protocol.

PROJECT TITLE: International Register of Scimitar Syndrome (SCIMITAR REGISTRY)
RAC#: 2151067

PRINCIPAL INVESTIGATORS: *Giovanni Di Salvo, MD*

PROJECT DESCRIPTION: Retrospective Longitudinal Study.

This study aims to create an international registry to collect data about patients with this rare syndrome (SCIMITR REGISTRY) with the aim of:

- Evaluate and compare the clinical condition in the natural history and after surgical correction
- Assess Clinical and Instrumental predictors for an unfavorable outcome
- Establish the criteria appropriate to the surgical correction

PROGRESS: Ongoing. Enrolled 36 patients in the study.

PROJECT TITLE: Failure of Tricuspid Valve Repair: Comparison of patients with and Without Transvalvular pacemaker or ICD leads
RAC#: 2121149

PRINCIPAL INVESTIGATORS: *Azam Shafquat, MD*

PROJECT DESCRIPTION: This is a case control study to determine the frequency of failure of TV repair in patients with a transvalvular pacemaker or ICD lead and to compare the results in patients without leads.

PROGRESS: Ongoing. Enrolled 38 patients in the study. Preparing for the analysis and Final report.

PROJECT TITLE: Left Ventricular Remodeling and Torsional Dynamics in Pediatric Patients with Dilated Cardiomyopathy
RAC#: 2121151

PRINCIPAL INVESTIGATORS: *Di Salvo Giovanni, MD*

PROJECT DESCRIPTION: This is a retrospective study to assess apical rotation in pediatric patients with dilated cardiomyopathy and to evaluate if reversed apical rotation is associated with more severe left ventricular dysfunction.

PROGRESS: Ongoing. Enrolled 59 patients in the study and 55 patient s in the current approval year. Abstract published in Echocardiography Journal.

PROJECT TITLE: Heart Centre Patients Functional Health Literacy
RAC#: 2121158

PRINCIPAL INVESTIGATORS: *ShisammaEmmanual, RN, BSN*

PROJECT DESCRIPTION: This is a cross-sectional survey to assess Heart Centre patients' functional health literacy level, determine where Heart Center patients seek healthcare advice, and determine Heart Center patients' preferred method for receiving healthcare information.

PROGRESS: Enrolled 147 patients in the study. Statistical analysis done and Final Report submitted. Our findings demonstrated that our health procedures are clear only for patients with university degree. Since 44% of our patients prefer to have the explanation by the help of audio visual materials, our findings suggest increasing the use of audio visual materials to make our patients more aware of the procedures or health teaching we perform. Increasing the awareness in patients reduces their anxiety and it will reduce the length of stay. This will lead to a better health care service to our patients.

PROJECT TITLE: The Predictive value of Heart Rate Variability in Critical Illness
RAC#: 2151069

PRINCIPAL INVESTIGATORS: *Bander Al Ghamdi, MD, Nawal Salahuddin, MD*

PROJECT DESCRIPTION: This is an Observational, prospective study combined with Heart Centre and Medical ICU team.

The aims of this study are:

1. To determine the predictive values of HRV measures for ICU admission
2. ICU and 28 day of mortality
3. Correlation of HRV with Vasopressor independence, lactic acid clearance, and organ dysfunction Scores.

PROGRESS: Ongoing. 56 patients have been enrolled.

PROJECT TITLE: Left Ventricle Longitudinal Systolic Shortening Index (LSI) and Right Ventricle Longitudinal Systolic Index (RSI), a Aew Echocardiographic Measurement, in Children
RAC#: 2141070

PRINCIPAL INVESTIGATORS: *Mohammad Naseruddin Moiduddin, MD*

PROJECT DESCRIPTION: A retrospective study to evaluate pediatric patients from January 1, 2009 to December 31, 2013 that had normal echocardiograms.

Aims of the study are:

1. Offer normal values for left ventricular longitudinal systolic index and right ventricular systolic index
2. To investigate whether these left ventricular longitudinal systolic and right ventricular systolic indexes would nullify the correlation of body surface area and age.

3. To investigate how these left ventricular longitudinal systolic and right ventricular systolic indexes correlate with published global LV and RV strain values respectively

PROGRESS: Enrolled 201 patients in the study. Statistical analysis done and final report submitted on June 2015. Abstract presented in Saudi Heart Symposium 2015. We determined that LSI is a reliable longitudinal measure of longitudinal left ventricular function that does not require Z-Scores. RSI is an additional reliable measure of longitudinal right ventricle function. We provide normal values for LSI and RSI. Age, Heart Rate, BSA, and gender do not affect LSI. Age does influence RSI in the few months. LSI can infer LV global longitudinal strain values. RSI can infer RV global longitudinal strain. Further studies using LSI and RSI on abnormal congenital heart lesions are warranted.

PROJECT TITLE: Prevalance, Clinical Characteristics and Outcomes of Patients with Heyde's Syndrome (Association Between Aortic Stenosis and Angiodysplasia) at KFSH&RC: Retrospective Review
RAC#: 2121077

PRINCIPAL INVESTIGATORS: *Bandar Al Ghamdi, MD*

PROJECT DESCRIPTION: This is a non-randomized retrospective study to identify: the frequency of Heyde's Syndrome in patients at the KFSH&RC; the course of angiodysplasia in aortic stenosis; whether any characteristics of aortic stenosis can predict the presence of angiodysplasia; and if there is an association between angiodysplasia and other valvular disease including mitral, tricuspid and pulmonary valve disease.

PROGRESS: Ongoing. From Echo data base 2635 patients has the diagnosis of Aortic Stenosis (AS) mild, moderate or severe. Screening done for all medical records. Out of this 108 patients had Endoscopy and 8 patients found to have Angiodysplasia. Waiting for the statistical analysis.

PROJECT TITLE: Central Venous Oxygen Saturation (Scvo2)/ Lactate Ratio as a Predictor of Major Adverse Event After Pediatric Cardiac Surgery: A Prospective, Observational Study
RAC#: 2101061

PRINCIPAL INVESTIGATORS: *Aly Makram Habib, MD*

PROJECT DESCRIPTION: The aim of this study is to assess whether central venous oxygen saturation (Scv02)/ lactate ratio is a reliable predictor of hospital mortality and major adverse event after pediatric cardiac surgery.

PROGRESS: Enrolled 143 patients in the study. Statistical analysis done and submitted the Final Report on October 2015. Using multivariate logistic regression, our results showed that ScVO2/ Lactate ratio predicted in-hospital mortality when done 3 hours after admission to CSICU from the OR (P=0. 05, CI: 0. 64- 1. 00). On the other hand, ScVO2/Lactate ratio didn't predict the occurrence of acute lung Injury, Brady arrhythmias that need pacemaker, Sudden cardiac death, nor need for ECMO in CSICU.

PROJECT TITLE: Pulmonary Embolism and Endarterectomy: The Saudi Arabian Experience
RAC#: 2141059

PRINCIPAL INVESTIGATORS: *Feras Khaliel, MD*

PROJECT DESCRIPTION: This is a retrospective study; the medical records of all the PTE patients from 1992 Jan 01 to 2013 Dec-31will be reviewed.

The aims of this study are:

1. To determine the outcomes of Pulmonary Endarterectomy (PTE) patients at KFSH&RC.
2. To compare the outcomes with reported literature outcomes of other centers.

PROGRESS: Ongoing. Enrolled 16 patients in the study.

PROJECT TITLE: A Retrospective Study to Determine the Outcomes of Bicuspid Aortic Valve After Surgical Repair in Pediatric Patients
RAC#: 2141050

PRINCIPAL INVESTIGATORS: *Giovanni Di Salvo, MD*

PROJECT DESCRIPTION: This is a retrospective study to review the medical records and echocardiography of pediatric patients who underwent cardiac surgery for aortic valve repair, excluding patients who underwent prior balloon aortic valvuloplasty, from January 01, 1998 and December 31, 2013.

PROGRESS: Ongoing. Filtered 279 patients' medical records and selected 34 patients who meet the study criteria. Started collecting the variables.

PROJECT TITLE: Outcome of Giant Coronary Artery Aneurysm in Kawasaki Diseased Patient in Saudi Arabia: Single Center Experience
RAC#: 2141049

PRINCIPAL INVESTIGATORS: *Abdullah Al Wadai, MD*

PROJECT DESCRIPTION: This is a cohort study consisted of children with Kawasaki disease who are treated at KFSH&RC, Riyadh, Saudi Arabia between January 1st 2000 to December 31st 2013. All included patients fulfilled the definition of Kawasaki disease using the diagnostic criteria.

The aims of this study are:

1. To assess the progression and outcome of coronary artery lesions (CAL) in Kawasaki disease patients at King Faisal specialist hospital and research center (KFSH&RC)
2. To evaluate the prevalence of different form of cardiac sequel among our patients.

PROGRESS: Ongoing. Enrolled 32 patients in the study.

PROJECT TITLE: Subvalvular Aortic Stenosis in Children: A 20-Years Single-Center Experience
RAC#: 2141034

PRINCIPAL INVESTIGATORS: *Abdullah AL-Sehly, MD*

PROJECT DESCRIPTION: A retrospective review with first echocardiography and follow ups and first surgery and redo surgeries, if any for all patients referred for Sub Aortic Stenosis (SAS) between 1st January 1993 to 31st December 2013 at KFSH&RC. The main purposes of this study.

To evaluate the clinical and surgical outcomes of patients with SAS And to determine the risk factors for recurrence from a major tertiary cardiac center experience Saudi Arabia.

PROGRESS: Ongoing. Identified 273 patients in the study. 164 patients meet inclusion criteria after initial screening. 16 patients data collected.

PROJECT TITLE: XANTUS-EL – Xarelto® on Prevention of Stroke and Non-central Nervous System Systemic Embolism in Patients with Non-valvular Atrial Fibrillation in Eastern EU, Middle East, Africa (EMEA) and Latin America (LATAM): A Non-interventional Study
RAC#: 2141024

PRINCIPAL INVESTIGATORS: *Kharabsheh Suleiman, MD*

PROJECT DESCRIPTION: Prospective non-interventional observational cohort (Phase IV) study of patients with non-valvular atrial fibrillation who are prescribed rivaroxaban under routine treatment conditions to prevent stroke or non-central nervous system systemic embolism. Patients will be followed up for 1 year or until 30 days after end of rivaroxaban therapy in case of therapy was discontinued earlier than 12 months.

The main goal of this non-interventional study is to confirm the known safety profile of rivaroxaban (Xarelto®), a new/novel oral anticoagulant in clinical practice use. The primary objectives are major bleeding, adverse events and total mortality. Secondary objectives include systemic thromboembolic events and non-major bleeding.

PROGRESS: Enrollment completed. Recruited 11 patients in the study. Continuing the follow up according to the protocol.

PROJECT TITLE: Commissural Malalignment Between the Aortic and Pulmonary Arteries in Transposition of Great Artery: An Echocardiography Study
RAC#: 2141023

PRINCIPAL INVESTIGATORS: *Abdullah AL-Sehly, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective study. The medical records of a patient who had under gone ASO from 1st January 2000 to 31st December 2013 will be reviewed. Aims of the study:

Determine the accuracy of echocardiography in preoperative detection of Commissural malalignment by comparing the results with the surgical findings. Determine the incidence of commissural malalignment in d-TGA and its Patterns in our patient population. Describe the frequency and patterns of associated coronary anomalies and other associated anomalies. Determine the impact of each pattern of commissural mal alignment and its associated anomaly on the surgical approach and its outcome.

PROGRESS: Ongoing. Identified 357 patients who meet the criteria. Started collecting data.

PROJECT TITLE: Utilization and Validation of the CHADS2 and CHA2DS2-VASc Risk Assessment Scores in Patients With Atrial Fibrillation at the Heart Centre, KFSH&RC
RAC#: 2141011

PRINCIPAL INVESTIGATORS: *Hassan Harbi, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective, study. The medical records of adult patients with non-valvular, chronic or paroxysmal atrial fibrillation will be reviewed. The aims are:

1. To assess the utilization by physicians of the CHADS2 and CHA2DS2-VASc scores in the decision to initiate antithrombotic therapy to prevent stroke in patients with atrial fibrillation.
2. To examine the current practices of physicians in treating atrial fibrillation and compare with American College of Cardiology and the European Society of Cardiology Guidelines.

PROGRESS: Ongoing. Enrolled 166 patients in the study and 84 patients in the current approval year.

PROJECT TITLE: Does Pulmonary Hypertension Affect Outcome After Mitral Valve Surgery
RAC#: 2141107

PRINCIPAL INVESTIGATORS: *Nedim Selimovic, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective, observational study of all patients who have undergone mitral valve surgery since January 2009 until December 2012 with follow up to December 2013. Pulmonary artery pressure was assessed by Doppler echocardiography pre- and postoperatively.

1. To evaluate impact of pulmonary hypertension (PASp ≥ 50 mm Hg) on:
   - Per- operative mortality
   - Early (30 days) survival
   - Long term survival following mitral valve surgery at KFSH&RC.
   - To assess effect of pulmonary hypertension on duration of hospital stay after mitral valve surgery.
2. To investigate differences in outcome in patients with isolated vs. combine valve surgery and existing preoperative pulmonary hypertension.
3. To observe influence of PH and identify possible differences in survival and other clinical parameters between patients undergoing primary (initial) vs. re-do surgery.

PROGRESS: Ongoing. Enrolled 233 patients in the study. Abstract presented in Saudi Heart Symposium 2015.

PROJECT TITLE: Establishing Gender Differences in the Incidence of CHD: Likelihood Based Approach
RAC#: 2141090

PRINCIPAL INVESTIGATORS: *Zohair Al-Halees, MD*

PROJECT DESCRIPTION: In this proposal we outline three objectives. First, we develop a multivariate probability distribution for the vector of binary observations based on a random sample of independent sib-ships. The vector will be split into two sub-clusters, including female and male responses respectively. The response variable is the number of siblings in each sub-cluster that possess a congenital heart defect of clinical interest. Here we consider several probabilistic models. The first model is a bivariate Poisson with over dispersion. The second is a bivariate negative binomial model. The advantage of the negative binomial is that the within sub-cluster over-dispersion can be accounted for in a natural way. The third model is the Sarmanov representation, which to the best of our knowledge has not been applied to data collected from families. The second objective is to construct the likelihood function of the sample based on the joint distribution of the created sub-clusters. This allows us to develop score and Wald chi-square-tests of significance that compare the levels of similarity among males and females from the same family. It is also suspected that consanguinity plays an important role in distribution of congenital traits. We account for the effect of consanguinity by two methods, the first is by considering it antecedent risk factor, and the second is by considering it a confounder. Finally, we illustrate our procedures using published data.

PROGRESS: Ongoing. Data included with 429 families. Consanguineos marriage 318 was and non-Consanguineous was 111. The analysis is based on the stratification of the data by consanguinity.

PROJECT TITLE: Outcomes of Patients with Reduced Left Ventricular Systolic Function Undergoing Heart Surgery at King Faisal Hospital & Research Centre
RAC#: 2141108

PRINCIPAL INVESTIGATORS: *Nedim Selimovic, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective, observational study. Aims are:

To study the basic demographic data of patients undergoing various cardiac surgeries with left ventricular systolic dysfunction and to identify the spectrum of various cardiac surgeries performed for patients with low ventricular systolic dysfunctions.

PROGRESS: Enrolled 209 patients in the study and statistical analysis done. Submitted the final report on September 2015. Renal impairment and severely reduced right ventricular function are independently risk factors for early and late mortality following cardiac surgery. Severe left ventricular systolic dysfunction does not appear to be an independent risk factor associated with higher mortality. Abstract presented in GHA in Kuwait 2015.

PROJECT TITLE: Echocardiogram Findings in Paediatric Patients with Mucopolysacharidosis At the KFSH&RC Heart Centre
RAC#: 2131043

PRINCIPAL INVESTIGATORS: *Nabil Ahmad AlQasimi, MD*

PROJECT DESCRIPTION: This is a retrospective, chart review. The aims are to characterize the echocardiographic abnormalities in children with different types of mucopolysaccharidosis and correlate survival with the cardiac involvement.

PROGRESS: Ongoing. Identified 75 patients in the study from 01 January 1999 to 31 December 2012 who were diagnosed with mucopolysaccharidoses. Collected the data for 55 patients and entered the data in data base.

PROJECT TITLE: The Role of Echocardiography in Selecting Pediatric and Congenital Heart Disease Patients for Resynchronization Therapy: A 4 years Follow up Study.
RAC#: 2131020

PRINCIPAL INVESTIGATORS: *Giovanni Di Salvo, MD*

PROJECT DESCRIPTION: This is a retrospective study. The aim is to assess in a long term follow-up study the predictive value of echocardiographic dyssynchrony parameters in CHD and pediatric patients who underwent CRT.

PROGRESS: Enrolled20 patients in the study and analysis done. Final report submitted on April 2015. Our findings suggest that the use of mechanical dyssynchrony, as assessed by SF, a simple qualitative M-mode derived parameter, in paediatric and CHD patients with systolic dysfunction would allow a better patient selection for CRT. Additionally, CRT appears to be a safe and valuable treatment in the long-term management of such patients. Abstract presented in multiple countries and published in Journal of Cardio vascular Medicine, International Journal Of Cardiovascular Research and Echocardiography.

PROJECT TITLE: ISHLT Mechanically Assisted Circulatory Support Registry (IMACS)
RAC#: 2131083

PRINCIPAL INVESTIGATORS: *Elias Saad, MD*

PROJECT DESCRIPTION: The primary goal of the IMACS Registry is to create, implement and analyze a registry that contains high standards for complete enrollment of patients who are placed on Mechanical Circulatory Support Devices (MCSD). The data allows participating hospitals to engage in important outcomes research about MCSD

PROGRESS: Ongoing. 5 patient's enrolled and 3 patients in the current report year.

PROJECT TITLE: Should Ross Procedure be Considered a Feasible Alternative for Adult Patients who Require AVR? Single Centre Patients' Long-terms Outcome, Clinical and Echocardiographic Study
RAC#: 2151082

PRINCIPAL INVESTIGATORS: *Pergola Valeria, MD*

PROJECT DESCRIPTION: This is a retrospective observational study. Five-hundred-thirty-two patients underwent the Ross procedure between January 1st 1990 and 31st March 2015. Clinical, echocardiographical, and surgical outcome data were determined from recent visit to our hospital. The cohort will be divided into 2 age groups at the time of surgery. Group 1 consist of younger patients less than or equal to 18 years of age and group 2 consist of patients older than 18 years.

Aim of the study is to:

- Evaluate the clinical and echocardiographic characteristic and the mid-long term results of the Ross operation in different groups of age and in different subset of patients (congenital vs Rheumatic)
- Evaluate the durability of the aortic auto graft and pulmonary homograft and the risk factors for re-operation.
- Analyse which are the criteria to create a score, to select ideal candidate, good candidate and not good candidates for this type of surgery.

PROGRESS: Ongoing. Patient enrollment started.

PROJECT TITLE: Does Open Heart Surgery Improve the Quality of Life in Octogenarian & Nonagenarian patients? 20 Years' Experience at the Heart Centre
RAC#: 2131084

PRINCIPAL INVESTIGATORS: *Feras Khaliel, MD*

PROJECT DESCRIPTION: This is a retrospective study. The aims of this study are to determine the quality of life after cardiac surgery in octogenarian & nonagenarian patients and to compare life expectancies in the post-surgical group with the predicted expectancies using the Euro SCORE, STS.

PROGRESS: Enrolled 92 patients in the study and statistical analysis done. Final report submitted on May 2015. Abstract presented in GHA in Kuwait 2015.

PROJECT TITLE: Diagnostic Value of Cardiac Computed Tomography Angiography in Patients with Left Bundle Branch Block and Abnormal Single Photon Emission Computed Tomography
RAC#: 2151105

PRINCIPAL INVESTIGATORS: *Bandar Al Ghamdi, MD, Ahmed Fathala, MD*

PROJECT DESCRIPTION: This is a retrospective study, combined with Heart center and Radiology department. Study looking for the subjects with known LBBB underwent both SPECT and CCTA (with a median of 65 days). Patients underwent SPECT on appropriate clinical indications. CCAC scanning was performed either on the basis of abnormal MPS and or presence of clinical symptoms. Exclusion criteria included a history of myocardial infarction, prior coronary bypass surgery or percutaneous coronary intervention, prior cardiomyopathy, or known Valvular heart disease.

PROGRESS: Ongoing. Enrolled 39 patients in the study.

PROJECT TITLE: Constant Treatment Dilemma in HOCM; Medical or Surgical?
RAC#: 2151006

PRINCIPAL INVESTIGATORS: *Feras Khaliel, MD*

PROJECT DESCRIPTION: This is a retrospective study and medical records of all the HOCM patients from 1st January 2003 to 31st December 2013 will be reviewed.

The aims of this study are:

1. To determine the outcomes of HOCM patients who received surgical management at KFSH&RC.
2. To compare and contrast our outcomes with patients managed medically and/or with a pacemaker.

PROGRESS: Ongoing. Enrolled 64 patients in the study.

PROJECT TITLE: A ClinIcal EvaluatioN of ST Changes in a Group of PatIents havinG Ventricular ArrHyThmias (inSighT)
RAC#: 2131067

PRINCIPAL INVESTIGATORS: *Bandar Al Ghamdi, MD*

PROJECT DESCRIPTION: This is a prospective, exploratory, multicenter, non-randomized investigation. The purpose is to determine the prevalence of device-recorded ST segment changes occurring before appropriate ICD therapies (ATP or Shock) and to define their temporal relationship to ventricular arrhythmias.

PROGRESS: Ongoing. Enrolled 12 patients in the study. All patients completed the 6 months follow up and 7 patients completed the one year follow up. Continuing the follow up as per the protocol.

PROJECT TITLE: Chronic Kidney Disease (CKD) Patients Undergoing Coronary Artery Intervention: Is CABG Superior to PCI?
RAC#: 2151118

PRINCIPAL INVESTIGATORS: *Aly Al Sanei, MD*

PROJECT DESCRIPTION: This is a retrospective review of patients who underwent CABG, and known to have CKD and undergone a CAD intervention (CABG Vs PCI).

The aims of this study are:

1. To calculate the mortality rate for both CABG and PCI in patients with CKD.
2. To determine the outcome of CABG in CKD patients, and compare with the Control group (CABG patients without CKD, in a matched propensity matter).
3. To evaluate the post-op progress of CAD in CKD Patients post CAD intervention.
4. Comparing the cohort group with the CKD patients who underwent PCI
5. Compare the outcome of PCI with CABG in renal dialysis patients

PROGRESS: Ongoing. Started to filter the patients.

PROJECT TITLE: Pregnancy and RHD: What are Possible Surgical Challenges
RAC#: 2141110

PRINCIPAL INVESTIGATORS: *Feras Khaliel, MD*

PROJECT DESCRIPTION: This is a retrospective study; the medical records of all the pregnant Valvular Heart Disease (VHD) patients will be reviewed. All women undergoing cardiac surgery during pregnancy and puerperium at Heart Centre from

1st January, 2000 to 31 May, 2014 will be included in the study.

The aims of this study are:

1. The feasibility of a safe cardiac bypass surgery in pregnancies over the elective patients
2. To determine bleeding and thromboembolic rate in Pregnant women with RHD
3. Comparison of outcome in patients who undergoes cardiac bypass surgery in pregnant woman under emergent situation vs. elective surgery.

PROGRESS: Ongoing.

PROJECT TITLE: Association Between cPRA & DSA (Luminex SA) with Hemodynamics, Rejection, Echocardiographic Parameters and Outcome in Heart Transplanted Patients
RAC#: 2151180

PRINCIPAL INVESTIGATORS: *Nedim Selimovic, MD, PhD*

PROJECT DESCRIPTION: This is a retrospective analysis study.

The purposes of this study are:

1. To determine incidence of Class I DSA (Donor specific antibodies), Class II DSA, Class I immunodominant DSA, Class II immunodominat DSA
2. To evaluate association between pre transplant DSA and hemodynamics, rejection, echocardiographic parameters and outcome in heart transplanted patients
3. Occurrence of antibody-mediated rejection (AMR) (12 months or longer); Allograft function at 3 years; Cardiac allograft vasculopathy at 3 years
4. To evaluate long-term survival and Cardiac Allograft Vasculopathy (CAV) development in patients with preformed DSA (Donor specific antibodies) and *de novo* DSA.
5. Specificity of human leukocyte antigens (HLA) typing in different groups of donors
6. To identify any differences in DSA(Donor specific antibodies) between different genders
7. Correlation between DSA MFI and CDC cross match
8. To investigate the clinical relevance of preformed HLA-DSA detected by SAB (Single HLA antigen coated beadssplantation) at the time of transplantation
9. To define HLA-DSA characteristics those are predictive for the occurrence of antibody-mediated rejection (AMR)

PROGRESS: Ongoing.

PROJECT TITLE: Early Experience with Subcutaneous Implantable Cardioverter-Defibrillators (S- ICD)
RAC#: 2151204

PRINCIPAL INVESTIGATORS: *Bandar Al Ghamdi, MD*

PROJECT DESCRIPTION: Retrospective data collection via patient's charts and pacemaker charts of S-ICD implanted from 01st September 2014 to 30th November 2015.

The aim of this study is to assess the learning curve for S-ICD implantation in our Heart Centre with respect to implant-related complications, and inappropriate shocks (IASs).

The S-ICD is relatively new and reviewing outcome of our patients with S-ICD would help in improving our knowledge about this system and help in choosing appropriate patients for this valuable but expensive device.

PROGRESS: Ongoing. Enrolled 22 patients in the study.

PROJECT TITLE: Incidence of Malignancies Occurring Post Heart Transplant: 8-year Following up the Overall Outcome & Rejection rate at KFSH&RC
RAC#: 2131114

PRINCIPAL INVESTIGATORS: *Feras Khaliel, MD*

PROJECT DESCRIPTION: This is a retrospective study. The aims are to determine the incidence of malignancy in post heart transplant patients, to compare the different types of malignancies in post heart transplant patients and to investigate the effect of malignancy on long term survival in post heart transplant patients.

PROGRESS: Enrolled 127 patients in the study and final report submitted after analysis. Despite the high ATG dosage used for induction, we surprisingly found a very low incidence (1. 5%) of malignancies post transplantation. One major contributory factor could be the relatively young age of our study population. In light of these results, we propose large scale genetic studies to be considered for our population. Abstract presented in GHA in Kuwait 2015.

PROJECT TITLE: The Correlation Between Pre-Existing Risk Factors and the Development of RV Dysfunction Following Surgery for Tetralogy of Fallot at the KFSH&RC
RAC#: 2131107

PRINCIPAL INVESTIGATORS: *Ghassan Siblini, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective, comparative study.

The aims of this study are:

1. To evaluate patients' echocardiograms and ECKs parameters at the age of 8-10 years of age post Tetralogy of Fallot repair.
2. To determine if a correlation exists between severe future right ventricular dilation and dysfunction at latest follow-up.

PROGRESS: Ongoing. Enrolled 38 patients in the study.

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- Di Salvo G; New Echo Techniques to Assess the Atrial Function; Cardiology Grand Rounds, King Abdul-Aziz Cardiac Center, King Abdul-Aziz Medical City; January 27, 2015.
- Di Salvo G; How To Assess Cardiac Function After Repair Of Aortic Obstruction In Adult Congenital Heart Diseases; Doppler Myocardial Imaging Course, Leuven, Belgium; February 5–6, 2015.
- N Moiduddin, J Kalloghlian, A Alshamaley; Fibrinolytic Therapy and Poly-Valvular Heart Disease in Pediatric Patients; Saudi Heart Association; February 13–16, 2015.
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- N Moiduddin, A A. Shati, S F. Mohammed, Z Y. Al Halees; A Female Neonate with Unguarded Mitral Valve Orifice; Saudi Heart Association; February 13–16, 2015.
- G. Di Salvo, Z. Al Bulbul, Z. Issa, BM. Fadel, G. Siblini, M. Al Fayyadh; Cardiac mechanics in patients after arterial switch operation: a speckle tracking echocardiography study; Saudi Heart Association; February 13–16, 2015.
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- R Said Abo El Ella; King Faisal Experience for Cardiac Surgery in Adults with Congenital Heart Disease: Outcome of primary and redo surgery; 64th ESCVS, Istanbul, Turkey; March 26–29, 2015.
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- G. Di Salvo, New Imaging Modalities in Heart Failure; Italian Society of Echocardiography, Napoli, Italy; April 16–18, 2015.
- Z Al Halees; Value Of Medical Technology To Patients And Health Care Systems; 6th Saudi Society For Respiratory Care Scientific Conference; April 07–09, 2015.
- G. Di Salvo, How to assess Atrial Function; New Imaging Modalities in Congenital Heart Disease Padova, Italy; April 9–11, 2015.
- M. Al Fayyadh; Device Therapy in Children and ACHD; 20th Asian Pacific society of cardiology congress, Abudabi, April 29–30, 2015.
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DEPARTMENT OF MEDICINE

DEPARTMENT OF MEDICINE

CHAIRMAN
Hamad AlAshgar, MD

THE DEPARTMENT OF MEDICINE AT KING FAISAL SPECIALIST HOSPITAL & Research Centre (KFSH&RC) continues to produce high caliber research projects. Research in areas of disease pathology, management, and prevention are part of the department commitment in conducting research proposals. The information generated has to undergo a peer-review process and organize in a format focused on improving patient care.

No less than 90 publications in peer-reviewed journals were published for the last 3 years and 23 projects were presented at the international meetings.

The Research Promotion Committee (RPC) of the department validates the scientific and ethical integrity of the research projects submitted by our staff. The objectives of the RPC consist of promotion of long-term plans to develop research with emphasis on community-oriented projects, and support participation of young researchers in major departmental projects.

We conducted a yearly research day celebration for the last 18 years. During the last 3 years, 36, 35 and 43 research projects were presented during 2013, 2014, and 2015 respectively. These undergo a thorough peer-review and top 3 projects from among the consultants and another 3 from trainees have received formal recognition. Many of these presentations have been accepted as international presentations and in peer-reviewed journals.

Department of Medicine greatly appreciated the generous donation of Dr Mohammed bin Saleh bin Abdulaziz Alrajhi amounting to Five Million Saudi Riyals as endowment to support research activities of the department. Part of its yearly revenue is being used, as per its By Laws, to fund the Alrajhi Laureate Awards and Grants for twelve outstanding projects which are divided into two categories – best 6 projects from consultants and best 6 projects from trainee's categories.

The Research Unit of the department was established in 2007 to support the research activities of our staff. Last 2015, His Excellency, Dr Qasim Al Qasabi has also donated Two Hundred Forty Thousand Saudi Riyals dedicated for research activities. The donated fund is governed by our Research Unit to support the grant-funded clinical research coordinators and other research-related projects. Criteria has been established in the utilization of the donation and the accountability report has to be approved by RPC and to be submitted to the Department Chairman and to CEO.

RESEARCH PROJECTS

PROJECT TITLE: Underlying Molecular Defects of Common Variable Immunodeficiency (CVID) and Hypogammaglobulinemia in Saudi Arabia
RAC# 2140 030
Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Rand Arnaout, MD*
CO-INVESTIGATORS: *H Al Dhekri, S Sumayli, A Al Ghonaim, B Al Saud, S Al Gazlan, F Sheikh, L Shekaili, D, Monis, N Altassan, M Abouelhoda*

SUMMARY: Common variable immunodeficiency is a primary immunodeficiency disorder characterized by impaired B cell differentiation with defective immunoglobulin production. It is the most prevalent form of severe antibody deficiency affecting both children and adults. "Variable" refers to the heterogeneous clinical manifestations of this disorder, which include recurrent infections, chronic lung disease, autoimmune disorders, gastrointestinal disease, and a heightened susceptibility to lymphoma. CVID is not a single disease, but rather a collection of hypogammaglobulinemia syndromes resulting from many genetic defects. In a small subset of patients, specific molecular defects have been identified; although in most cases, these causes are as of yet, unknown.

Common variable immunodeficiency (CVID) is estimated to affect as many as 1 in 25,000 individuals but it is far more common in our community (29%; 450/100,000) because of intermarriages and consanguinity. Age of onset is typically after puberty and before 30 years of age, with some evidence of a bimodal distribution demonstrating peaks between 1 and 5 years, and 18 and 25 years. The clinical manifestations of CVID affect multiple organ systems, and patients often have been evaluated by several specialists by the time they are diagnosed. Perhaps partly for this reason, delayed recognition of this disease is common.

Although CVID has been recognized since the 1950s, its pathophysiology remains incompletely understood despite dramatic advances in the molecular elucidation of many other primary immunodeficiency diseases. Approximately 90 percent of patients with CVID appear to have disease that has resulted from a sporadic mutation, while 10 percent of patients have at least one family member with either CVID or selective IgA deficiency and demonstrate a familial pattern of inheritance (both autosomal dominant and autosomal recessive). Several genetic defects have

been demonstrated in patients with CVID, each of which affects the normal processes of B cell maturation and differentiation into memory B cells.

In our study we screened all patients in KFSHRC diagnosed to have CVID, hypogammaglobulinemia or selective IgA deficiency for the presence of known or novel molecular defects in an effort for early diagnosis through genetic studies and possible gene therapy once available. This will help in reducing complications, mortality and preventing the disease inheritance by family counseling regarding consanguineous marriages. Interestingly, the recognition of molecular defects in CVID will help in determining the phenotypic presentation and severity of the diseases which will guide us in early diagnosis and prognosis

OBJECTIVES:

- To investigate the epidemiology of known and unknown molecular defects in patients presented with clinical features constant with CVID and hypoagammaglobulinemia or IgA defeciency in Saudi Arabia.
- To assess the link between the presence of these defects with disease clinical presentation, clinical course, complications, response to immunoglobulins and overall prognosis.
- In cases where loci linked to known genes are excluded, we will search for novel candidate genes using linkage analysis and homozygozity studies using Cyto2, Axiom and/or 6.0 Affymetrix Microarray DNA chips, or pedigrees of familial cases with at least 1 past or current affected mamber.
- Whole genome sequencing approach will be conducted such as Exome sequencing if the identified lesion by linkage analysis and homozygozity mapping is too large and a candidate gene/s cannot be identified.

FUTURE OBJECTIVES:

- To provide gametoselection if accepted by the patient and family for HSCT.
- To study the possibility of gene therapy for affected patients in an effort to cure their disease

PROJECT TITLE: Outcome Allogenic Hematopoietic Stem Cell Transplantation in Autosomal Recessive Hyper-IgE Syndrome Due to DOCK8 Deficiency: Single Center Experience

RAC# 2151 134

Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Rand Arnaout, MD*

ABSTRACT: Hyper-IgE syndrome, a primary combined immunodeficiency characterized by a triad of eczema, recurrent severe skin and pulmonary infections with markedly increased levels of serum IgE.

Mutation analysis in this family found to have 2 mutations one is a novel pathogenic mutation, leading to a severe and progressive disease, the other mostly non-pathogenic, both involving the DOCK8 gene

In this report, we discuss these three related Saudi patients, their clinical presentation, their disease complication and fatal outcome. On the other hand, we report successful allogenic bone marrow transplantation in one of the three family members with an excellent outcome and reversal of all clinical manifestations

RESULTS: Sequence analysis identified two copies of missense mutation, c.4346C>T, in the coding region of the DOCK8 gene in all patients. This sequence variant, c.4346C>T, predicts an amino

acid change of serine (S) to Leucine (L) at codon 1449 of the DOCK8 protein (p.S1449L). This sequence variant is of unknown significance as it has not been reported, and is predicted to be benign and tolerated. However, they carry mutation in different splice site at position 5 after the end of axon 45 and the effect of the splice site mutation has not been reported previously. However, from this mutation no Dock8 protein was detected by western blot. Thus absence of the DOCK8 expression is significant and apparently pathogenic.

PROJECT TITLE: The Impact of Glycemic Control and Disease Duration of Type 2 Diabetes on Vitamin D Status and Other Components Metabolic Syndrome
RAC# 2151 144
Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Nora Alkahtani, MD*
CO-INVESTIGATORS: *Thuraya Alaidrous, Mahmoud M. Abulmeaty*

AIM OF THE STUDY: The purpose of this study is to correlate the effect of Glycemic Control and Disease Duration in Type 2 Diabetes on Vitamin D Status and other Component of Metabolic Syndrome among Saudi patients.

STUDY DESIGN AND SETTING: A case control studies will be conducted at King Faisal Specialist Hospital & Research Centre in Riyadh.

SAMPLE SIZE: Sample size 125 participants, with 100 cases (subdivided into 4 groups of 25 patient each) and 25 controls. Sample size was calculated by using online calculator for sample sizes, at 95% of two-sided confidence interval and 80 % power (% chance of detecting); the % of healthy controls exposed to T2DM = 20% according to international Diabetes Federation IDF data about KSA and the % of cases with Vitamin D deficiency (VDD) exposed to T2DM ≈ 83% (Taheri, et al 2012), thus the odd ratio will be 19.53 and sample size will be 12-22 cases.

The inclusion criteria: The study will include 25 healthy participants and 100 confirmed type 2 diabetic patients by their history. The accepted age range for both genders will be 18 to 60 year.

EXCLUSION CRITERIA:

- Participants diagnosed with type 1 diabetes and who had a history or evidence of parathyroid or calcium related diseases, history or evidence of endocrine diseases including hyperthyroidism, hypothyroidism, adrenal disease, and pituitary disease; neurological disease; renal disease; diabetic nephropathy, pregnancy or who are currently breastfeeding; vitamin D supplementation or any drugs affecting calcium and vitamin D metabolism, as judged by the investigating physicians.
- The control group will be free of bone disease, diabetes, cardio metabolic risk and of similar age, gender and demographic data.

PROJECT TITLE: Efficacy of Direct Acting Anti-Viral Agents for the Treatment of Chronic Hepatitis C Infected Saudi Patients: A Real-Life Experience
RAC# 2151 160
Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Musthafa Peedikayil, MD*
CO-INVESTIGATORS: *Mohammed Al Quaiz, Fahad Al Sohaibani, Hamad Al Ashgar, Khalid Al Kahtani, Abdulrahman Al Fadda, Mohammed Khan, Ahmed Aljedai*

ABSTRACT: Chronic hepatitis C infection and related liver disease are very common in Saudi Arabia. Different directly acting antiviral agents (DAA) are available for the treatment of HCV infection. King Faisal

Specialist Hospital and Research Centre has a large cohort of HCV-infected patients. Though we have been treating HCV-infected patients with DAA since 2014, there are no data available from Saudi Arabia on its efficacy. The real-life data can be different from the results that are available from licencing drug trials. Hence, we are proposing a retrospective study to find the sustained virological response of chronic HCV-infected patients treated with any treatment regimen that has used any of the DAA in any combination with FDA-approved anti-HCV drugs.

OBJECTIVES

- To find out the sustained virological response (SVR) at 12 weeks and 24 weeks post treatment of chronic HCV patients treated with any regimen that has used an FDA approved directly acting antiviral agent (DAA).
- To find the relapse rate after achieving sustained response at 12 weeks in patients treated with DAA.
- To identify the effective treatment regimen that works the best for the Saudi population infected with HCV
- To find any relation between SVR and baseline characteristics of the patient, viral load at 2 week and 4 weeks after starting the treatment.
- To assess the ALT and AST response to DAA treatment.

INCLUSION CRITERIA:

- Patients should be 18 years old and above.
- Any patient with chronic HCV infection and who have received any of the DDA in combination with any accepted anti-viral agent.
- Patients should have a measurable HCV viral load in IU/ml before starting HCV treatment with DAA.
- They should have HCV viral load tested at the end of the treatment, after 12 and preferably 24 weeks of treatment.
- The patient should have taken at least 80% of the medications given to them.
- As assessment of the liver fibrosis should be available with either fibro scan, liver biopsy, ultrasound liver or other imaging modalities.
- The information on underlying medical conditions, liver function, cirrhosis, and liver transplant status should be available.
- If the patient had previous treatment for HCV, then the details of drug regimens used, the response to treatment, and the reason for discontinuations of the treatment regimen should be available.
- If the patient discontinued treatment regimen with DAA, then the reasons for discontinuations should be collected.

EXCLUSION CRITERIA:

- Patients with incomplete data where we cannot judge on treatment regimens, completion of the treatment, and the treatment response.
- Post liver transplant patients
- Post renal transplant patients

PURPOSE AND SIGNIFICANCE OF THIS STUDY

- The proposed study will give us information on the efficacy of newly introduced DAA for the treatment of chronic HCV. Often, real-life data is different from the data obtained from licencing trials. KFSHRHC has a significant cohort of chronic HCV population. Given the availability of various new medications for HCV treatment, it has become essential to know which regimens are most suitable and cost effective for the Saudi population. Also, the current study will give us information the treatment response with new DAA medications on real life patients with different co-morbid illnesses. The proposed research will be a

benchmark study and definitely will guide the physician in the management of chronic HCV infection that is a common health problem in Saudi Arabia.

PROJECT TITLE: Osteoporosis and Chronic Liver Disease in Saudi Arabia: A Case-control Study
RAC# 2151 202
Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Fahad Al Sohaibani, MD*
CO-INVESTIGATORS: *Hamad Al Ashgar, Khalid Al Kahtani, Mohammed Al Quaiz, Abdullah AlKhenizan, Faisal Aba AlKhail, Mohammed Khan, Ibrahim Muhsen, Omar AlFraihi, Sultan AlSaud*

ABSTRACT: Chronic liver disease (CLD) is a major cause of morbidity and mortality. The management of CLD requires attention to its complications. Literature had shown that osteoporosis is one of the major complications of CLD; however, no studies to our knowledge have been done to investigate the association between CLD and osteoporosis in Saudi Arabia. Given that, the prevalence of CLD and osteoporosis in Saudi Arabia are high, we aim to conduct a case control study that to look at the prevalence of osteoporosis in patients with CLD compared with general population and give some insights on the effect of different hormones on that. The study will involve 51 CLD patients of chronic viral and fatty liver etiologies and 51 age and gender matched control, the duration of the Study will be 12 Months.

STUDY AIMS:

The study aims for the following:

- Investigate the prevalence of osteoporosis in patients with moderate-severe chronic liver disease (Child-Pugh score B and C, see Table 4) due to chronic viral hepatitis (B and C) and NAFLD.
- Identify the main risk factors for the development of osteoporosis among CLD patients including e.g. Age, gender, menopausal status, degree and type of cirrhosis.
- Give some insights on the association between different hormones and osteoporosis and different risk factors that might play a role in increasing the risk of getting osteoporosis.

PROJECT TITLE: Venous Thrombosis in Patients Undergoing Hyperthermic Intraperitoneal Chemotherapy (HIPEC)
RAC# 2141081
Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Aamir Sheikh, MD*
CO-INVESTIGATORS: *Ayman Azzam, Hakeam Hakeam, Shahad Raslan,Abdulaziz Al Onazi, Rariq Amin*

AIM OF THE STUDY: To report the incidence of venous thrombosis post hyperthermic intraperitoneal chemotherapy (HIPEC) with splenectomy, for the management of patients with peritoneal carcinomatosis from variable tumor origin.

PRIMARY AND SECONDARY END POINTS: The primary endpoint of this study is to report the incidence of the development of symptomatic and asymptomatic venous thrombosis (pulmonary embolism (PE) and deep vein thrombosis (DVT)), within one month following HIPEC with splenectomy.

PROJECT TITLE: Anticoagulation of Behcet's Disease with Thrombosis: A Series of 34 Cases in a Tertiary Care Centre in Saudi Arabia (Data collection)
RAC# 2151126
Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Muneerah Albugami, MD*

CO-INVESTIGATORS: *Ahmed Alshiek, Abdelazeim Elamin, Mohammed Siddiquee, Usamah El Alem, Hanan Alhazmi*

OBJECTIVE: We will report our experience in long term anticoagulation of Behcet's disease with thrombosis.

STUDY DESIGN: A descriptive retrospective chart review study of 34 patients of Behcet's disease with thrombosis on long term anticoagulation. In this study, we will report the main characteristics, treatment, and long-term outcomes of Behcet's disease with thrombosis on anticoagulation.

INCLUSION CRITERIA: All adult (age >14 years) Behcet's disease patients had followed up in the anticoagulation clinic at KFSH&RC.

SAMPLE: Patients are identified from the registry of thromboembolic disorders at KFSH&RC.

PROJECT TITLE: Attitude of Medical Residents Toward the Geriatric Patients
RAC# 2151183
Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Muneerah Al Bugami*

BACKGROUND: Globally, the number of elderly (aged 65 years or over) is expected to be from 841 million people in 2013 to be more than 2 billion in 2050. The older persons aged 80 years or over are14% in 2013 and are projected to reach 19 % in 2050. The dramatic increase in the elderly population expected over the next few decades will place a heavy strain on the current health care system. As the number of elderly increases, there is a great demand to teach and train physicians in geriatric medicine. There are concerns that physicians in training are not learning adequate geriatric medicine to prepare them for the rapidly expanding numbers of elderly. Existing literature on the attitudes of medical trainees toward elderly shows a wide difference from negative to positive.

OBJECTIVE: To describe the attitude of medical residents toward geriatric patients at King Faisal Specialist hospital & Research Centre (KFSH&RC).

METHOD: It is a cross-sectional survey which contains 29 questions distributed to medical residents at KFSH&RC during the academic day. Each question has multiple-choice options. Completion of the questioners is voluntary.

CONCLUSION: Medical residents have negative attitude toward geriatric patients. The information from this study showed there is a need for comprehensive geriatric medicine curriculum in medical collages and residency programs in Saudi Arabia to improve attitudes, knowledge and skills in the care of the geriatric patients. Improvement the teaching and training in geriatric medicine will help to overcome the negativity that resident express toward geriatric patients.

PROJECT TITLE: Carbapenem Versus Beta-Lactam/ Betalactamase Inhibitor Combination Therapy for Blood Stream Infections Caused by Extended-Spectrum Beta-Lactamase (ESBL)-Producing Enterobacteriaceae: A Retrospective, Cohort Study
RAC# 2151 163
Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Dr A Omrani*
CO-INVESTIGATORS: *Dr N Mukhtar, Dr L Albalawi, Dr S Althawadi, Dr M Shoukri, Dr A Alrajhi, et al*

OBJECTIVE OF STUDY: To compare the clinical effectiveness of empiric therapy with a carbapenem versus BL-BLI inhibitor combination for blood stream infections

caused by ESBL-producing Enterobacteriaceae in terms of:

- 30-day, all-cause mortality (primary end-point)
- Microbiological response; ie, negative follow up blood cultures (secondary end-point).
- Days to microbiological response (secondary end-point).
- Length of hospital stay after initiation of carbapenem or BL-BLI therapy (secondary endpoint).
- Length of ICU stay after initiation of carbapenem or BL-BLI therapy (secondary end-point).

METHODS This will be a single-center, retrospective, cohort study.

INCLUSION CRITERIA:

- Age ≥ 14 years.
- ESBL-producing Enterobacteriaceae from ≥ 1 blood culture; susceptible to piperacillintazobactam at current CLSI MIC breakpoints.
- Receipt of ≥48 hours of empiric piperacillin-tazobactam or carbapenem (ertapenem, imipenem or meropenem) within 48 hours before or after collection of the index positive blood culture.

EXCLUSION CRITERIA:

- Receipt of piperacillin-tazobactam or carbapenem (ertapenem, imipenem or meropenem) within 7 days prior to onset of clinical signs of sepsis.
- Concomitant receipt of an agent with in-vitro activity against microorganism causing BSI (e.g.; quinolone, aminoglycoside, co-trimoxazole, etc).

STUDY DESIGN AND PATIENTS: Consecutive, non-repetitive patients with blood stream infection caused by ESBL-producing Enterobacteriaceae will be identified through KFSH&RC microbiology database. Demographic, clinical, radiological and laboratory data will be retrieved from patients' charts and the hospital's integrated clinical information system. Data will include:

- Demographics
  - Age
  - Gender
- Clinical details:
  - Source of infection.
  - Date of hospitalization and discharge or death.
  - Details of any invasive procedures within 14 days prior to first positive blood culture (e.g.; central venous access, arterial blood access, urinary catheterization, invasive diagnostic or therapeutic procedures).
  - Charlson Co-morbidity Score22 - (Appendix 1)
  - Pitt Bacteremia Score4 - (Appendix 2)
  - Bloodstream Infection Mortality Risk Score (BSIMRS) 23,24 - (Appendix 3).
  - Acute Physiology and Chronic Health Evaluation (APACHE) II Score; for patients admitted to intensive care unit (Appendix 4).
  - Daily clinical parameters whilst on therapy.
  - All concomitant antimicrobial therapy.
- Microbiological data:
  - Date of first positive blood culture with ESBL-producing organism.
  - Dates and results of subsequent blood cultures (up to 14 days after discontinuation of therapy or death)
  - Dates and results of all microbiological cultures within 14 days before start of therapy

- Dates and results of all microbiological cultures up to 14 days after date of discontinuation of therapy or death.

STATISTICAL ANALYSIS: The primary endpoint is 30-day mortality. Secondary end-points include:

- Time to microbiological response.
- Length of hospital stay after initiation of BL-BLI or carbapenem.

The primary endpoint will be compared using Kaplan-Meier curves and log-rank test. A sample size of 170 patients, 85 in each arm, will provide an 80% power for detection of non-inferiority at a margin of -10%. P values of <0.05 will be considered statistically significant. The propensity score, the probability of receiving carbapenem as empirical therapy, will be calculated using a non-parsimonious multivariate logistic regression model in which the outcome variable is the use of carbapenem as empirical therapy. Multivariate analysis will be performed by Cox regression, using time until death as the dependent variable and therapy with BL-BLI or carbapenem as the explanatory variable of interest. Potential confounders and interactions will be added using a forward method. The propensity score for receiving a carbapenem as empirical therapy will be added to the model. SPSS (SPSS; version 15.0) will be used for all statistical analyses.

PROJECT TITLE: Molecular Characterization, Epidemiology, Risk Factors and Outcomes of Carbapenem Resistant Gram Negative Infections

RAC# 2150 021

Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Dr A Omrani*

CO-INVESTIGATORS: *Dr L Albalawi, Dr N Mukhtar, Dr S Althawadi, Dr M Shoukri, Dr A Alrajhi, et al*

OBJECTIVES:

- To identify risk factors associated with CRE blood stream infections in King Faisal Specialist Hospital and Research Centre (KFSHBRC).
- To characterize the molecular mechanisms mediating carbapenem resistance in CRE isolates from KFSH&RC.
- To describe the molecular epidemiology of CRE blood stream infections in KFSH&RC including any clustering or cross-infection
- To define factors associated with CRE treatment failure and mortality.

PATIENTS AND MATERIALS: Consecutive, non-repetitive, Enterobacteriaceae isolated from blood cultures during the period from January 1,2010 to May 31,2015 will be identified through electronic search of computerized microbiology database at KFSH&RC. Cases are defined as patients aged 214 years with CRE from blood cultures taken at KFSH&RC. Controls will be selected from patients aged 214 years with carbapenem-susceptible Enterobacteriaceae from blood cultures. Cases and controls will be matched on 1:2 ratio for month of hospitalization, bacterial species and source of infection. The following data will be retrieved from the patients' charts and electronic records:

- Demographics:
  - Age.
  - Gender.
  - City of residence.
- Clinical and Epidemiological Data:
  - Source of hospital admission (i.e., planned admission, emergency department, transfer from other institutions, etc.)
  - All patient locations with dates. All hospital admissions within the preceding 12 months including hospital name and address, and ICU stays with dates.

- Source of infection.
- Date of hospitalization and discharge or death.
- Charlson Co-morbidity Score40 (Appendix 1)
- Pitt Bacteremia Score4' (Appendix 2)
- Bloodstream Infection Mortality Risk Score (BSIMRS) **Id3 (Appendix 3).
- Acute Physiology and Chronic Health Evaluation (APACHE) II Score; for patients admitted to ICU (Appendix 4).
- Daily clinical parameters whilst on antimicrobial therapy for index episode of blood stream infection.
- All invasive procedures within the preceding 90 days including urinary catheterization, central line access, any surgery or invasive diagnostic procedures with dates, location and complications.
- All systemic antimicrobial therapy within the preceding 90 days with dates.
- Details of any cancer chemotherapy within the preceding 90 days.
- Details of any immunosuppressive therapy within the preceding 90 days.
- Details of any solid organ or HSCT

PROJECT TITLE: Risk Factors for and Outcomes of Infections Caused by Carbapenem and Colistin-Resistant Gram Negative Bacteria: A Matched-Control Study
RAC# 2151 162
Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Dr A Omrani*
CO-INVESTIGATORS: *Dr Y Aljishi, Dr M Alkathlan, Dr S Althawadi, Dr M Shoukri, Dr A Alrajhi, et al*

OBJECTIVES:

- To describe the clinical course and outcomes of patients with colonization or infection caused by carbapenem and colistin resistant Gram-negative bacteria.
- To identify risk factors associated with the isolation of carbapenem and colistin resistant Gram negative bacteria.

DESIGN: Matched, retrospective, case-control study.

PATIENTS AND MATERIALS: An electronic search of computerized microbiology database at KFSH&RC will be performed to identify all Enterobacteriaceae, A. baumannii and Pseudomonas species isolated from anybody site during the period from January 1, 2010 to September 30, 2015.

INCLUSION CRITERIA FOR CASES:

- Patient aged ≥14 years
- Isolation of Gram-negative bacteria resistant to imipenem, meropenem and colistin from culture of anybody site over the study period.

INCLUSION CRITERIA FOR CONTROLS:

- Patients aged ≥14 years
- Gram-negative pathogen susceptible to imipenem, meropenem and colistin isolated from culture of anybody site over the study period.

MATCHING: Cases and controls will be matched on 1:3 ratio for:

- Bacterial species
- Site of isolation (i.e.; specimen type)
- Month of isolation

PROJECT TITLE: Access Flow Based Intervention for Management of Arteriovenous Hemodialysis Access Dysfunction (FBI trial). A Prospective Randomized Controlled Study
RAC# 2151 040
Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Naveed Ul Haq, MD*
CO-INVESTIGATORS: *Mohammed Althaf, Mohammed Abdelsalam, Mamdouh Albaqumi, Lutfi Al Korbi, Mohammed Shoukri.*

SPECIFIC AIMS: In a randomized, controlled, blinded trial we would like to assess the clinical utility of an access flow based intervention approach as compared to conventional approach for managing dialysis arteriovenous access dysfunction.

STUDY DESIGN: Prospective, Randomized Controlled, single centre trial comparing access flow based intervention versus conventional standard approach for dialysis access dysfunction.

STUDY SUBJECTS: ESRD patients on HD or referred for access dysfunction to the interventional nephrology service at King Faisal Specialist Hospital and Research Center in Riyadh, KSA.

INCLUSION CRITERIA:

- Age >18 years
- Patients with access dysfunction secondary to stenosis anywhere in the AVF.

EXCLUSION CRITERIA:

Patients with following characteristics will be excluded from the study:

- Patients on anti-coagulation and those with bleeding disorders
- Life expectancy less than 12 months.
- Documented severe contrast allergy.
- Inability to come for timely and adequate follow up.
- Patients undergoing transplantation work up and expected to be transplanted within 6 months.
- AVG with access dysfunction developing within 30 days of surgery.
- AVF with early fistula failure.
- Recurrence of stenosis within 3 months of previous intervention.

PROJECT TITLE: Drug-Eluting Balloon angioplasty for Early Fistula Failure (DEBEFF) Trial
RAC# 2150 054
Source of Funding: KFSH&RC

PRINCIPAL INVESTIGATOR: *Naveed Ul Haq, MD*
CO-INVESTIGATORS: *Mohammed Althaf, Mohammed Abdelsalam, Samer Koussayer MD, Mohammed Abdulrahman AlGhonaim, MD, FRCP(C),FACP*

SPECIFIC AIMS: To assess the efficacy of DEB angioplasty in AVF with EFF as compared to standard PBA.

STUDY DESIGN: Prospective, blinded, randomized, controlled, single centre trial comparing DEB angioplasty to current standard PBA angioplasty.

Endpoints of the study are as follows:

Primary Endpoint: Primary un-assisted patency of the AVF at 6 months
Secondary Endpoints: Maturation rate, time to maturation, secondary or assisted patency at 6 months, number of procedures required to maintain patency, average access flows, number of thrombotic episodes.

OUTCOME OF STUDY: This study aims to assess whether DEB angioplasty is no an inferior intervention compared to PBA angioplasty in patients with early fistula failure. Outcome is maturation of AVF that had early fistula failure. Assessment of maturation of AVF will be done when the following criteria are met.

- 1 session of hemodialysis is completed with successful cannulation

- Minimum blood flow of 300 ml/min on dialysis
- Acceptable arterial and venous pressures on dialysis

STUDY SUBJECTS: ESRD patients on HD or CKD patients ready to start dialysis regardless of gender referred for access failure to the interventional nephrology service at King Faisal Specialist Hospital and Research Center in Riyadh, KSA

INCLUSION CRITERIA:

- Age >18 years
- Patients with EFF
- Cause of EFF secondary to stenosis anywhere in the AVF.
- On confirming EFF the patients will be randomized to either group by virtue of blockrandomization.

EXCLUSION CRITERIA:

Patients with following characteristics will be excluded from the study:

- Patients with AVF which is deeper than 0.8cm from the skin.
- AVF which is tortuous and lacks adequate straight segment for cannulation with 2 needles.
- Patients with allergy to paclitaxel
- Patients on anti-coagulation and those with bleeding disorders.
- Severe thrombocytopenia i.e platelet count< 50,000.
- Life expectancy less than 12 months.
- Documented severe contrast allergy.
- Inability to come for timely and adequate follow up.
- Patients undergoing transplantation work up and expected to be transplanted within 6 months.
- EFF secondary to accessory veins

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NEUROSCIENCES

NEUROSCIENCES

CHAIRMAN

Imad Kanaan, MD

THE DEPARTMENT OF NEUROSCIENCES' MISSION AND VISION ARE state of the art tertiary neuroscience clinical care, research and education. Department of Neurosciences research endeavors encompass several clinical registries, basic, clinical translational research and technical innovations. These are conducted in collaboration among its four sections, multi-disciplinary clinical programs, King Faisal Specialist Hospital & Research Centre, national and international academic institutions.

Neuroscience research activities are supported by approved RAC projects and reflected in several publications in peer review journals.

The department is composed of four sections: The Section of Adult Neurology; the Section of Pediatric Neurology; the Section of Neurosurgery; and the Section of Clinical Neurophysiology.

RAC APPROVED PROJECTS

SECTION OF ADULT NEUROLOGY

PROJECT TITLE: The Impact of Co-Morbities on Severity of Epilepsy in Elderly
RAC# 2151 093

INVESTIGATOR: *Madiha Al Hubayshi, MD*

PROJECT DESCRIPTION: To evaluate the effect of the presence of comorbidities on the severity of seizure in 60 year old patient and above in the Saudi Arabia KFSH&RC as the incidence of epilepsy is now higher than before.

PROGRESS: Ongoing.

PROJECT TITLE: ICTAL EEG as Predicting for Vagal Nerve Stimulation Outcome in Patients with Intractable Epilepsy
RAC# 2151 164

INVESTIGATOR: *Salah Baz, MD*

PROJECT DESCRIPTION: To identify the prognostic importance of different ICTAL EEG patterns obtained during Video EEG monitoring on surgical outcome in patients with intractable Epilepsy undergoing Vagal Nerve Simulation (VNS).

PROGRESS: Ongoing.

SECTION OF PEDIATRIC NEUROLOGY

PROJECT TITLE: Tuberous Sclerosis Complex: Clinical Spectrum and Epilepsy. A retrospective Chart Review Study
RAC# 2151 057

INVESTIGATOR: *Hesham Al Dhalaan, MD*

PROJECT DESCRIPTION: Review of clinical data and epilepsy associated with TSC of all patients diagnosed at KFSH&RC.

PROGRESS: Ongoing.

PROJECT TITLE: Leukodystrophies in Saudi Arabia Retrospective King Faisal Specialist Hospital & Research Centre Experience
RAC# 2151 060

INVESTIGATORS: *Aziza Chedrawi, MD and Mohamed Al Muhaizea, MD*

PROJECT DESCRIPTION: Retrospectively review the clinical data of this group of patients. Such information will shed light on this group of diseases that is probably more common in this part of the world due to its recessive inheritance. It will hopefully set the stage for establishment of clinical diagnostic guidelines and in that sense improve therapeutic measures by early treatment implementation whenever possible or empower counselling and preventative measures by increasing awareness of the medical community in the nation.

PROGRESS: Ongoing.

SECTION OF NEUROSURGERY

PROJECT TITLE: Clinical Safety Study on 5-Aminolevulinic Acid In Children and Adolescents with Supratentorial Brain Tumors
RAC# 2151 088

INVESTIGATOR: *Essam Al Shail, MD*

PROJECT DESCRIPTION: Primary Study Aim – To determine clinical and toxicological safety by determining the incidence of adverse events CTCAE Grade III, IV and V during intra-operative fluorescence-imaging

of contrast-enhancing supratentorial brain tumors (e.g. PNET, GB, AA, ependymomas) using 5-ALA.

SECONDARY STUDY AIM: *a)* To determine the positive predictive value of 5-ALA for identifying tumor, defined as the number of fluorescing biopsies containing tumor cells divided by the number of all fluorescing biopsies; *b)* Degree of resection, determined as the volume of contrast-enhancing tumor on early post-operative MRI after a prior definition of whether complete resection would be aim of surgery; *c)* Determine 5-ALA pharmacokinetics in children and adolescents, as assessed from PPIX plasma level 6, 12 and 24 hours after administration of 5-ALA provided that parents or guardians agree to blood sampling. Blood sampling is purely on a voluntary basis and independent of study participation.

PROGRESS: Ongoing.

SELECTED ACHIEVEMENTS

- Launching of "Brainsuite" Intraoperative Magnetic Resonance Imaging Facilities
- MCA Diamond Awards 2015:
  1. Patient Care Story of the Year (A Blind Man)
  2. Innovation/New Technology (Brain Suite Facility)
  3. Research Award – Saeed Bohlega, MD
- Awareness Day:
  1. Brainhealth Awareness Day – 03 April 2015
  2. The Purple Day Epilepsy Awareness Day – 16 April 2015
  3. Parkinson's and Movement Disorder Awareness – 18 May 2015
- Workshop:
  4. Neurophysiology (EEG/IOM) and Epilepsy Workshop – 26-27 August 2015

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DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

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The Department of Obstetrics and Gynecology at King Faisal Specialist Hospital and Research Center, Riyadh is a tertiary care center providing up-to-date evaluation and management in Maternal-Fetal Medicine, Reproductive Endocrinology and Infertility, and Gynecologic Oncology patients.

Our multidisciplinary medical staff consists of 15 consultants, 1 associate consultant, 5 assistants, 12 fellows, 18 KFS&RC sponsored residents and 5 outside sponsored residents who have special qualifications and experience in dealing with high risk antenatal cases, difficult gynecology and obstetrics surgical procedures, and provide care for couples with infertility problems and those with a variety of genetic disorders through a dedicated pre-implantation genetic diagnosis program.

The department is composed of three sections: Maternal Fetal Medicine (MFM), Reproductive Endocrinology and Infertility (REI), Gynecology and Gynecologic Oncology.

The Section of MFM handles all types of high risk pregnancies with fetal and maternal complications. The Infertility/IVF Unit performs the latest Assisted Reproductive Technologies (ART) from conventional IVF to all types of micromanipulation techniques. Pre-implantation Genetic Diagnosis (PGD) is one of the unique hi-tech services offered by IVF unit. The Division of Gynecologic Oncology delivers an up to date care to women with all types of gynecologic malignancies. The services include cancer screening, early diagnosis as well as surgical and medical management of all gynecologic cancer cases.

RAC APPROVED PROJECT

PROJECT TITLE: Retrospective Review of the First Single-Center Experience from Saudi Arabia with Laparoendoscopic Single-Site Surgery (LESS) for Management of Benign Gynecologic Adnexal Pathologies

Project Code: 2151 114

INVESTIGATORS: *Ismail A. Al-Badawi (PI), Osama AlOmar, Naryman Albadawi, Ahmed Abu-Zaid*

BACKGROUND: Minimally invasive surgery (MIS)—laparoscopy—is evolving as the standard of care for the management of various benign and malignant adnexal gynecologic conditions. The advantages of laparoscopic surgery over laparotomy have been well-documented through various retrospective studies and prospective randomized controlled trials. Such advantages include: reduced post-operative morbidity, pain, hospitalization, as well as rapid post-operative recovery, better quality-of-life, superior cosmesis, and improved surgical outcomes.

One of the ground-breaking advances in MIS is the introduction of laparoendoscopic single-site surgery (LESS). As opposed to the conventional laparoscopy that is often performed by using three to five small incisions (5–20 mm each), LESS uses only one small skin incision of the umbilicus to completely perform the laparoscopic surgical procedures.

In a recent systematic review of all LESS-related articles, only around 9% of all reviewed articles were related to gynecologic procedures. Although there are still limited data and solid conclusions regarding the use of LESS in gynecologic procedures, the currently available published data have shown feasibility, safety and reproducibility

of LESS for managing numerous gynecologic conditions.

AIMS:

- To review the feasibility of LESS in the management of various benign gynecologic adnexal conditions.
- To review safety of LESS in the management of various benign gynecologic adnexal conditions
- To review the pre-operative, intra-operative and post-operative details and outcomes of LESS procedures
- To review previous literature about LESS in gynecologic surgery.

PROJECT TITLE: Retrospective Review of a Single-Center Experience with Routine Prophylactic Ureteric Stents Placement Before Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy (HIPEC)
Project Code: 2151 113

INVESTIGATORS: *Ismail A. Al-Badawi (PI), Tarek Amin, Mohammed AlOtaibi, Osama AlOmar, Ayman Azzam, Ahmed Abu-Zaid, Hussam Abou Al-Shaar*

BACKGROUND: Iatrogenic ureteric injury is a serious operative adverse event in abdominal and pelvic procedures. Particularly, gynecologic surgeries roughly account for 75% of all ureteric injury cases. The occurrence of ureteric injury in gynecologic surgeries is not uncommon, with an incidence rate approximately ranging from 0.2% to 2.5%. Moreover, about 70% of all gynecologic-related ureteric injuries go unnoticed in the operating room, and mostly diagnosed in the post-operative period, with an estimated average interval of 1 to 3 weeks from the time of surgery to the clinical diagnosis.

This increased risk of ureteric injuries in gynecologic surgeries can be largely attributed to the naturally occurring anatomic vicinity and embryologic connection between the urinary, genital, and gastrointestinal tracts. Ureteric injuries most frequently take place at the levels of suspensory ligament of ovary, angles of vagina, and around uterine blood vessels.

Many authors advocated that meticulous surgical exploration of the retroperitoneal space and subsequent direct visual identification of the ureters is the ideal method to prevent ureteric injuries. However, direct visual identification of ureters can be very challenging in managing patients with primary or recurrent disseminated intraperitoneal gynecologic malignancies, who are referred to complex procedures such as cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). In such CRS plus HIPEC procedures, abdominopelvic adhesions, tumor-related ureteric infiltrations, aggressive dissections, and extended lymphadenectomies are implicated prior to exposing the ureters and internal structures. Consequently, ureters are at increased operative risks of direct mechanical, chemical and thermic insults. Possible mechanisms of direct mechanical ureteric injury include: incidental resection of a segment of ureter, ischemia from ureteral stripping or electrocoagulation, angulation of ureter with secondary obstruction, crushing, ligation with a suture, and possibly others. Furthermore, Sugarbaker did not mention the use of prophylactic ureteric stenting neither in his earliest description of total peritonectomy plus HIPEC, nor in the subsequent review of his case study.

Previous studies demonstrated that prophylactic ureteric stenting can effectively identify the ureters in major debulking gynecologic surgeries,

and consequently reduce the risk of operative ureteric injury and related morbidities. Herein, we report our single-center experience (feasibility and morbidity) with routine prophylactic ureteric stenting in CRS & HIPEC in managing primary advanced or recurrent peritoneal carcinomatosis from gynecologic malignancies.

AIMS:

- To review the feasibility of using prophylactic ureteric stents as routine procedure before cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) in managing peritoneal carcinomatosis (PC) from gynecologic malignancies.
- To review the outcomes, morbidities of this procedure
- To review the incidence of ureteric and genitourinary injuries in this group of patients.

PROJECT TITLE: Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Management of Peritoneal Sarcomatosis: A Preliminary Single-Center Experience from Saudi Arabia
Project Code: 2161 039

INVESTIGATORS: *Ismail A. Al-Badawi (PI), Tarek Amin, Ayman Azzam, Abdullah Alsuhaibani, Osama AlOmar, Ahmed Abu-Zaid, Lynn Alkhatib, Mohammed Abuzaid, Tusneen Elhassan*

BACKGROUND: Soft tissue sarcomas (STSs) are quite rare neoplasms accounting for roughly 1% of all adult solid malignancies. Approximately 30% to 36% of all STSs originate in the retroperitoneum or abdominopelvic cavity. The natural biological behavior of STSs is characterized by an increased tendency for disease dissemination and recurrence. Modes of disease dissemination include: local invasion, peritoneal infiltration, blood-borne and rarely lymph-borne spread. Around 35% to 82% of all STSs will experience disease recurrence after the initial surgical management. The vast majority of these recurred STSs (80%–90%) will progress and present as peritoneal sarcomatosis (PS) — multinodular intraperitoneal dissemination of STS. Also, it should be recognized that PS may be the primary presentation in a proportion of patients.

Prognosis of patients with primary or recurrent PS is generally poor with an estimated median overall survival ranging from 6–15 months. Current therapeutic modalities such as surgery, radiotherapy, and chemotherapy are largely ineffective against PS. Therefore, an aggressive loco-regional approach in management of patients with PS and no extraperitoneal disease has been suggested. There is a universally agreed consensus that aggressive loco-regional management of PS requires a well-studied comparison between cytoreductive surgery (CRS) alone, and combined modalities (combination) of CRS plus hyperthermic intraperitoneal chemotherapy (HIPEC).

The combination of CRS plus HIPEC has been employed successfully in loco-regional management of peritoneal mesothelioma as well as peritoneal carcinomatosis arising from epithelial ovarian, non-epithelial ovarian, endometrial, appendiceal (pseudomyxoma peritonei), colorectal and gastric cancer origins. The use of CRS plus HIPEC in management of primary or recurrent PS remains a subject of controversy, and is limited by a few numbers of studies with variable outcomes.

AIMS:

- To review the feasibility of CRS+HIPEC in the management of PC.
- To review safety, morbidity and mortality of CRS+HIPEC in the management PC.

- To review the pre-operative, intra-operative and post-operative details and outcomes of CRS+HIPEC in the management of PC.
- To calculate disease-free survival and overall survival, and perform univariate analysis to predict prognostic variables (to be done by a biostatistician).
- To review previous literature about CRS+HIPEC in the management of PC.

PROJECT TITLE: Human Papillomavirus (HPV) Viral Load and E6/E7 mRNA Expression as Predictive Markers for the Development of Cervical Carcinoma
Project Code: [RAC # 2130033]
Source of Funding: KACST 13-MED2127-20

INVESTIGATORS: *Fatimah S. Alhamlan, Mohammed N. Al-Ahdal, Ahmed A. Al-Qahtani, Tarfah A. Al-Muammar, Ismail A. Al-Badawi, Asma M. Tulbah, Maha Tulba, Abdullah Alkhenizan, Aneela Hussain, Marium Ahmed*

OVERVIEW: Human papillomavirus (HPV) infection has been considered as a significant etiological factor and an important prognosticator in cervical cancer. Our central hypothesis is that the viral load of HPV and E6/E6 mRNA expression will increase with disease progression such that the viral load and oncogene expression will gradually increase in cervical samples displaying cytology consistent with less severe disease (ASCUS to LGSIL) to more severe disease (HGSIL) and, finally, to cervical carcinoma. Since the disease progression with an HPV infection usually takes 10–15 years, we have proposed to choose a cross-section of patients who have normal cytology but are HPV positive, as well as those with ASCUS, LGSIL, HGSIL and cervical cancer. Our specific aims are to examine cervical specimens from participating Saudi women for normal and abnormal cytology, and identify the stages of abnormal cytology according to the Bethesda classification, identify HPV DNA through PCR amplification of the L1 gene and genotype HPV positive results by using a bead-based multiplexing Luminex assay, Sequence the whole HPV genome to establish phylogenetic analyses of HPV strains in a Saudi population, perform and standardize an HPV viral load assay in cervical specimens and elucidate the role of this viral load in the progression of HPV-related diseases, and perform a quantitative real-time reverse transcription PCR assay that detects and quantifies E6/E7 oncogene mRNA to determine whether these oncogenes may be predictive markers for the development of cervical carcinoma.

PROJECT TITLE: The Prognostic Impact of Human Papillomavirus (HPV) Genotypes on Cervical Dysplasia and Cancer. A Retrospective Cross-sectional Study
Project Code: RAC# 2150001
Source of Funding: Submitted to GSK

INVESTIGATORS: *Fatimah S. Alhamlan, Asma M. Tulbah, Ismail A. Al-Badawi, Mohammed N. Al-Ahdal*

OVERVIEW: Cervical cancer is the second most frequent cancer in women worldwide, with approximately 530,000 new cases and 275,000 deaths reported throughout the world in 2008 (World Health Organization [WHO]). The main goals of the proposed study are to determine the prevalence of HPV and its genotypes in Saudi Arabia and to understand the prognostic impact of these HPV genotypes on cervical dysplasia and cancer. There are three specific aims: To examine the correlation between HPV presence and disease progression in a hospital-based cohort (i.e., KFSHRC), to demonstrate the expression of the E6 oncogene in each disease stage and its association with disease progression, and analyze the overall survival rate (OS) of HPV-infected patients.

Our results may also alert the public and the appropriate government agencies to the prevalence of HPV and assist in the decision to recommend HPV screening, triage, and vaccination, as well as aid in the prediction of the disease progression. In this era of individualized medicine, the treatment of HPV infection may well become personalized based upon HPV types that are common in our country.

PROJECT TITLE: Understanding the Role of Surfactant Protein SP-A and SP-D in Normal and Preterm Labor
Source of Funding: Submitted to KACST # 77-36-AT

INVESTIGATORS: *Fatimah S. Alhamlan, Mohammed N. Al-Ahdal, Ismail A. Al-Badawi, Wesam Kurdi, Manal Mustafa*

OVERVIEW: Understanding normal labor fully at term is central to prevention and management of preterm labor. Birth defects and preterm birth are the leading causes of infant mortality and there is a clear association between the two. Moreover, preterm birth makes a significant contribution to medical disabilities, e.g. cerebral palsy, and long term adverse social outcomes in the surviving infants. More research is necessary into the mechanism of parturition in order to prevent spontaneous preterm labor and improve neonatal outcome. Surfactant proteins SP-A and SP-D are innate immune molecules secreted by the fetal lung into the amniotic fluid, which are considered to be important in labor via activation of the prostaglandin pathways and cytokine secretion in the fetal membranes and decidua. In this project, we propose to use full length native and truncated SP-A and SP-D molecules and examine if they alter prostaglandin and cytokine release in placental tissues obtained before and after term and preterm labor. We will also correlate the mechanisms via local expression of SP-A, SP-D, prostaglandins, oxidative stress markers, and angiogenic factors in human placenta and decidua and compare their expression between normal and preterm labor pregnancies. These experiments will help dissect events in the decidual and fetal membranes involved in the onset of labor at term, and highlight possible physiopathological changes in preterm labor, and lead to better measures to reduce adverse perinatal outcomes.

PROJECT TITLE: National Screening of Human Papillomavirus Prevalence and Type-distribution in Saudi Arabia (Multi-Central Based Study)
Source of Funding: Submitted to KACST

INVESTIGATORS: *Fatimah S. Alhamlan, Mona Al-Mushait, Ismail A. Al-Badawi, Mohammed N. Al-Ahdal, Tarfah A. Al-Muammar, Asma M. Tulbah, Wesam Kurdi, Ali Azahrani*

OVERVIEW: Human papillomavirus (HPV) infection is a significant etiological factor and prognosticator of cervical cancer, with high-risk HPVs playing a role in the development of over 70% of recorded cervical cancer cases. However, most Saudi women and even some Saudi healthcare professionals are unaware of the risks associated with high-risk HPV type infections. Cervical cancer risk can be reduced by detecting lesions that may become invasive cervical cancer, typically through cytology testing. Although cytology testing has markedly reduced the number of reported cervical cancer cases in developed countries over the past few decades, the World Health Organization estimates that 561,200 new cancer cases (5.2% of all new cancers) are attributable to HPV infection. Thus, many developed countries now also include HPV testing during primary health screens for women, as HPV is present in 99.7% of cervical squamous carcinomas. In contrast to developed countries, no HPV screening programs have been conducted in Saudi Arabia. In addition, data on the prevalence of HPV in Saudi Arabia, which to date have been

derived from only individual hospital-based efforts remain controversial. Therefore, the overall goal of the proposed project is to conduct a national HPV screening that will include women living in all 13 provinces of Saudi Arabia. Cervical specimens will be obtained from 10,000 women attending hospitals throughout the country and sent to KFSHR Riyadh for cytology (i.e., Papanicolaou or Pap smear) and HPV-DNA testing and genotyping. Our results will provide an accurate estimate of the HPV genotypes and their prevalence in Saudi Arabia. Our HPV prevalence data will inform the decisions of the Ministry of Health and other government agencies about the necessity of HPV screening, triage, and vaccination programs. Lastly, because studies have shown that most Saudi women are unaware of either the importance of Pap testing or the association of HPV with cervical cancer, our proposal will provide a national HPV and cervical cancer awareness campaign.

PROJECT TITLE: Detection of Genes Causing Polycystic Kidney in Saudi Arabian Fetuses and Neonates

INVESTIGATORS: *M. H. Al-Hamed, W. Kurdi, Z. Abdullah, M. Tulbah, M. Al-Nemer, R. Khan, N. Al-Sahan, M. Albaqumi*

OVERVIEW: Polycystic kidney disease (PKD) is common in the Saudi population and is associated with significant morbidity and mortality. Recent reports estimated the prevalence of PKD in Saudi population to be 0.57 per 1000 births. The majority of polycystic disease in fetuses arises from recessively inherited mutations of genes expressed in the primary cilium of renal epithelial cells. To investigate the genetic basis of polycystic disease in Saudi families, we recruited forty fetuses presenting with PKD diagnosed by ultrasound. Molecular karyotype to exclude aneuploidy was negative for all cases. Sequencing of the following genes (PKHD1, NPHP1, INVS, NPHP3, NPHP4, IQCB1, CEP290, GLIS2, RPGRIP1L, AHI1, CC2D2A, MKS1, TCTN2, TMEM67, and TMEM216) resulted in identification of molecular causes of PKD in 16 cases (40%). Mutations of the CC2D2A gene are most common and account for 44% of mutations detected. Mutations in the CC2D2A gene are always associated with cystic kidneys and Encephaloceles indicating Meckel-Gruber syndrome diagnosis. Novel mutations in INVS and TCTN2 genes were detected. Oligogenic inheritance has been observed in two families. A third family had homozygous mutation in TMEM67 gene and another homozygous mutation in the RPGRIP1L gene. These types of inheritance (Oligogenic and homozygosity in two Cilia genes) are likely aggravating the phenotype.

PROJECT TITLE: Health Literacy and Behaviour of Women During Preconception and Pregnancy
RAC# 2151 117

INVESTIGATORS: *W. Kurdi, S. R. Mikler, S. Javed, S. Kalantan*

OVERVIEW: The primary purpose of the proposed research is to gain understanding of how young women living in Saudi perceive pre-conception and prenatal health as it related to birth outcomes. The survey will focus on young mother's knowledge on the importance of nutrition; diet that is rich in micronutrients and vitamins in particular folic acid; physical activity and maintaining good health. Major changes in the food choices and eating habits progressively have become more "westernized", in recent years and being blamed for the rising rates of overweight and obesity among population in Saudi culture. The primary research question of the proposed work is to assess the preconception, prenatal behavioral of mothers and their impact on childbirth outcomes: In general, a) how do women living in Saudi Arabia obtain their knowledge on health related matte? b) How important are social factors (e.g. family networks

and socio-economic status) in providing women access to health care? C) How does cultural context influence health literacy?

PROJECT TITLE: Are Blood Groups Associated with the Ovarian Reserve and the Outcome of *In Vitro* Fertilization Treatment?

INVESTIGATORS: *Khalid A Awartani, Rahma AlGhabshi, Hanan AlShankiti, Mohammed AlDossari, Serdar Coskun*

OBJECTIVES: The association between ABO blood groups and ovarian reserve in infertile patients has been a point of controversy. The aim of this study was to assess the correlation of certain blood groups with ovarian reserve and response to the treatment in patients undergoing infertility treatment.

PROJECT TITLE: Intramuscular Progesterone (Gestone) vs Vaginal Suppository (Cyslogest) for Luteal Phase Support in Cycles of *In Vitro* Fertilization (IVF): Patient Preference and Drug Efficacy

INVESTIGATORS: *Amal Zaman, Mohammed Ergsoas, Ahmad Alsanei, Serdar Coskun, Khalid Awartani*

BACKGROUND: Following IVF treatment, patients are routinely given progesterone supplementations for luteal phase support. In our program it is given for an average of 8 weeks in form of either Intramuscular progesterone 50mg daily injections, or vaginal cyclogest suppositories 400mg BID based on patient's preference. We observed patients demand on more IM preparations, while there is a worldwide shortage in supply of the IM progesterone. The objective of our study is to assess the patient's preference regarding the routes of progesterone supplementation and their satisfaction with the selected choice, and Compare the efficacy of the different routes.

AIMS: Prospective cohort study, patients < 40 years old undergoing IVF treatment at our clinic were offered to participate. Patients were allocated by their choice to either group A (the vaginal progesterone), or group B (IM progesterone). Both groups were treated similarly apart from the progesterone intervention. A satisfaction score from 1-5 was used to assess patients satisfaction in regard to the treatment method, they were interviewed for recording of their satisfaction and the side effects. Sample size was calculated for a total of 409 patients.

PROJECT TITLE: Antenatal Complications and Pregnancy Outcome After Sleeve Gastrectomy—Case Control Study at KFSH&RC

INVESTIGATORS: *Qamariya Ambusaidi, Maha Tulbah, Sana Tulbah*

ABSTRACT: Obesity is well known risk factor for pregnancy related complications including infertility, miscarriages, hypertension, pre-eclampsia, diabetes, abnormal fetal growth, preterm delivery and operative delivery. WHO reported that an estimated of more than 1.4 billion adult is obese and > 50% of them are female. Overall, more than one in 10 of the world's adult population is obese, with Middle East, Pacific Islands, Southeast Asia, and China being the areas at greatest risk. In Saudi Arabia, obesity is increasing with an overall prevalence of 35.5%; in comparison, females were significantly more obese than males with a prevalence of 44% and 26.4%, respectively.

Bariatric surgery (BS) has become more frequent among women especially child bearing age group. Sleeve gastrectomy is the comments performed procedure in Saudi population. In this procedure, the surgeon removes 75% of the stomach. Although it is a restrictive procedure, it results

in marked reduction of neuroendocrine function and enzymes secretion. The most common deficiencies encountered are iron and vitamin B12 defficiency. Therefore there is higher rate of intrauterine growth restriction and small babies.

The best timing for pregnancy post bariatric surgery is not known but most surgeons suggesting delay pregnancy for 2 years. In multicenter study in Spanish by Gonzale et al result showed in pregnancies occurring during first year of BS a higher rate of stillbirth and small babies. In another study rate of anemia was 24.2% and vitamin B12 was deficient in 13.3% after sleeve gastrectomy.

Neonates after bariatric surgery had significantly lower average birth weight without a higher frequency of low birth weight defined as< 2.5 kg at term. A comparison of neonatal data between babies born before surgery and siblings born after surgery showed that after surgery newborns had lower average birth weight with no significant differences in body length or head circumference and no cases of macrosomia.

The objective of this study is to study the maternal and fetal complications in women post sleeve gastrectomy in comparison to normal pregnant women.

AIMS:

- To estimate the prevalence of iron and vitamin B12 deficiency
- To estimate the incidence of growth restriction in newborns
- To compare the incidence of developing gestational hypertension, diabetes, adverse fetal outcome, preterm delivery and operative delivery

PUBLICATIONS

- Al-Badawi IA, AlOmar O, AlBadawi N, Abu-Zaid A, Retrospective review of the First Single-Center Experience from Saudi Arabia with Laparoendoscopic Single-Site Surgery (LESS) for Management of Benign Gynecologic Adnexal Pathologies (accepted in-press).
- Al-Badawi IA, Amin T, AlOtaibi M, AlOmar O, Azzam A, Abu-Zaid A, Al-Shaar HA Retrospective Review Of A Single-Center Experience With Routine Prophylactic Ureteric Stents Placement Before Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy (HIPEC) (published).
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OPHTHALMOLOGY DEPARTMENT

OPHTHALMOLOGY DEPARTMENT

CHAIRMAN

Selwa Abdullah Al-Hazzaa, MD,FRCS

MEMBERS

Dr. Saad Al-Haddab, *Consultant*
Dr. Faisal Al-Qahtani, *Consultant*
Dr Amal Al-Malki, *Consultant*
Dr. Jeylan El-Mansoury, *Consultant*
Dr. Maaly Abdelfataah, *Assistant Consultant*
Dr. Musa Al-Zayed, *Senior Optometrist*
Miss. Amani AL-Jassas, *Optometrist*
Mr. Abdulaziz Al-Zoba, *Clinical Research & Statistical Coordinator*

THE OPHTHALMOLOGY DEPARTMENT AT KING FAISAL SPECIALIST Hospital & Research Center (KFSHRC) continuously strive to enhance the quality of life for those we serve by improving sight and preventing blindness through competent and compassionate patient care, innovative research and continuing education. We also seek to advance the knowledge and skills of fellow Ophthalmologists, clinicians and trainees who will form the next generation of practitioners.

The Ophthalmology Department has a history of international clinical research in eye diseases and is involved in several ongoing departmental and inter-departmental projects. These projects and studies will play a major role and contribute in understanding the natural course of eye diseases, the outcome of treatment and the epidemiology and genetics of eye diseases and vision loss in the Kingdom of Saudi Arabia.

At the end of 2015, our department has three (3) international Publications and five (5) RAC-approve on-going projects. One of the department's main goal and mission is to expand descriptive and investigative research in the upcoming years in collaboration with the research center and the other departments at KFSH&RC and other institutes.

RESEARCH PROJECTS

PROJECT TITLE: Evaluation of Macular Changes After Uneventful Phacoemulsification Surgery in Diabetic Patients Using Optic Coherance Tomography
RAC# 2141006

PRINCIPAL INVESTIGATOR: *Dr Maaly Abdulfattah, Assistant Consultant*
CO-INVESTIGATORS: *Dr Selwa Al-Hazzaa, Consultant, Dr Faisal Al-Qahtani, Assistant Consultant*

Cataract surgery is well known to elicit postoperative mocular adema. The exact mechanism is not knownn but the role of surgical trauma and release of protaglandin are suspected.

AIMS: The aim of our study is to measure the meann foveal thickness after uneventful phacoemulsification and posterior chamber IOL implementation using optical Coherance Tomography.

PROGRESS: On-going (revising the data and finalizing the report).

PROJECT TITLE: Ophthalmic Consultation in a Large Specialized Hospital
RAC# 2141040

PRINCIPAL INVESTIGATOR: *Dr. Jeylan El-Mansoury, Consultant*
CO-INVESTIGATOR: *Dr. Selwa Al-Hazzaa, Consultant, Dr. Maaly Abdelfataah, Assistant Consultant*

AIMS: To profile all in-patients and ER consultations evaluated and managed by the Ophthalmology Department at KFSH&RC (Managed by Consultants and Assistant Consultants) will be documented and the information collected since late 2014 will be analyzed according to the following categories: Age, Service requesting Consult, Reason for consult, type of consultation and the final diagnosis.

PROGRESS: Ongoing (working on the final report).

PROJECT TITLE: Visual Impairment and Blindness in Saudi Arabia
RAC# 2141044

PRINCIPAL INVESTIGATOR: *Amani Al-Jassas, Optometrist*
CO-INVESTIGATOR: *Dr. Selwa Al-Hazzaa, Consultant, Dr. Maaly Abdelfataah, Assistant Consultant*

AIMS: To determine the cause of visual impairment and blindness in the Saudi population as represented by the countrywide referrals to KFSH&RC as we lack data that fully represents the whole population or reflects any changes since the first study in 1986.

A current and representative epidemiologic study is essential to determine the full range of cause of visual incapacity in the Saudi population. The Ophthalmology Department at KFSH&RC is well-placed to conduct this study since it has a broad catchment area, receiving referrals from all regions of the kingdom and has the man power, expertise and multi-disciplinary support to make appropriate diagnosis. While contributing to a global database for incidence, prevalence and trends in visual impairment and blindness, knowledge gained from this study will assist locally, to provide a platform for assignment of resource, streaming management for better quality of care and assist in designing public health awareness campaigns for the prevention and early diagnosis of vision loss.

PROGRESS: Ongoing (Analyzing Data and preparing the final report).

PROJECT TITLE: Efficacy of AMBLYZ for treatment of Mild Amblyopia
RAC# 2141045

PRINCIPAL INVESTIGATOR: *Amani Al-Jassas, Optometrist*
CO-INVESTIGATOR: *Dr. Selwa. Al-Hazzaa, Consultant*

AIMS: To determine the efficacy of the new Amblyz liquid crustal glasses for the treatment of strabismic amblyobia at KFSH&RC. Refraction and provision of glasses and occlusion of the healthy eye to encourage development of the amblyopic eye is usually employed and has been documented to help c, the most frequent of which is adhesive patching children regain vision. Several methods are currently in common use. Where this is not possible, blurring of the healthy eye or penalization is achieved by optical or Cycloplegia. The major drawback to these therapeutic investigations is the stigma suffered by the child, who may be non-compliant while is at school or otherwise unsupervised. Other unintended consequences include skin irritation from patch and decreased vision in the cycloplegically penalized eye. A new device, Amblyz has been developed to overcome these shortcomings. These liquid crystal glasses can have the appropriate refractive correction and have an electronically, controlled, intermittent occlusion of the sound eye while allowing for adequate visual stimuli to the amblyopic eye.

PROGRESS: Ongoing (revising the abstract and the data).

PROJECT TITLE: Education in Glaucoma in a Tertiary Hospital in Saudi Arabia
RAC#2141065

PRINCIPAL INVESTIGATOR: *Dr. Jeylan El-Mansoury, Consultant*
CO-INVESTIGATOR: *Dr. Selwa Al-Hazzaa, Consultant, Dr. Maaly Abdelfataah, Assistant Consultant*

AIMS: To profile the knowledge of all glaucomatous patients about their disease and its treatment in the department of Ophthalmology at KFSH&RC. The broader goal was to learn about factors that affect how glaucoma patients care for themselves, and even more broadly, to understand how to promote the health of patient's non-compliance with prescribed drug regimens is a major obstacle to the treatment of chronic diseases including glaucoma. The long term treatment of this asymptomatic condition provides no subjective improvement, is expensive and maybe associated with unpleasant side effects. All those factors contribute to discourage patients from using the medication that have been prescribed. It has been reported that glaucoma patients have little understanding of their disease and its treatment, but no study assessing this information was conducting in KFSH&RC. Furthermore, the information derived will be helpful in determining any need for staff and resource allocation and stream-lining of screening protocols that might serve to improve quality of patient care.

PROGRESS: Ongoing (revising the final report).

PROJECT TITLE: Retinal Nerve Fiber Layer Thickness in Alzehimer Disease
RAC# 2151010

PRINCIPAL INVESTIGATOR: *Dr. Selwa Al-Hazzaa, Consultant, Fatima BoQoied, Optometrist*
CO-INVESTIGATOR: *Dr. Najeeb Qadi, Consultant*

AIMS: To investigate retinal fiber layer thickness in patients with alzehiemer disease without visual impairment using optical coherence tomography and to compare the results with healthy control. Visual symptoms have been reported in the early stages of alzehiemer disease, including difficulties reading, finding objects, depth perception, and perceiving structure from motion, color recognition and spatial contrast sensitivity. This study will

examine the relationship between alzehiemer disease and the anterior visual pathway.

PROGRESS: Ongoing (collecting and analyzing data).

PUBLICATIONS:

- *Journal of Neuro-ophthalmology* - Pub # 2130287, "Bilateral Optic Nerve Sheath Metastases from Signet Cell", Jan 2015. Dr Selwa Al-Hazzaa, Dr Joyce Mbekeani.
- European Medical Genetic Journal – " Variable expression Pattern in Donnie –Barrow Syndrome: report of two novel LRP2 mutations and review of the Literature" May, 2015. Dr Selwa Al-Hazzaa, Dr Maaly Abdulfattah, Dr Ola Khalifa.
- Comprehensive Gene Panels provide Advantages over clinical Exome Sequencing for Mendelian diseases: Fowzan S. Al-Kuraya, Selwa A. Al-Hazzaa. Accepted" *Genome Biology*", GBIO-D-00057R3, June 2015.
- *Nature Cell Biology* – Pub # NCB-J27740C " An siRNA- based functional genomics screen for the identification of regulatores of cilogenesis and ciliopathy genes" June, 2015. Fowzan S. Al-Kuraya, Selwa A. Al-Hazzaa.
- *Journal of Hematology/Oncology & Stem Cell Therapy* – Pub # 2130286, "Papillary Tumor of the Pineal Region Presenting with Foster Kennedy Sign" June 2015. Dr Joyce Mbekeani, Dr Selwa Al-Hazzaa, Dr Maher Hassounah.

ACHIEVEMENTS

- Introducing the use of the Anti –VEGF- Aflibercept (Eylea).
- Introducing upper lid crease surgical approach for superior orbitotomy.
- The usage of Tacrolimus topical ocular surface treatment of Management of GVHD patients

ORGAN TRANSPLANT CENTER

ORGAN TRANSPLANT CENTER

DIRECTOR

Prof. Dieter Broering, MD, PhD, FEBS

THE ORGAN TRANSPLANT CENTER (OTC) WAS ESTABLISHED ON October 2010. It is one of KFSH&RC's division which focuses on providing world leading transplantation healthcare. It is also one of the most active and experienced transplant centers in the Middle East.

Research within the Organ Transplant Center is a collaborative effort with the Research Centre of KFSH&RC and focuses on translational, epidemiological and clinical research in organ conditioning, tissue engineering, tolerance induction, medical and surgical innovations and stem cell research.

The advancement of interdisciplinary research within the OTC and the development of the Organ Transplant Registry will enable the translation of our findings to clinical settings which could potentially have a significant clinical impact on the improvement of health, quality of life and life expectancy for transplant recipients and donors. The development of excellent education and research will help the OTC to continue providing exceptional healthcare for kidney, liver, lung, pancreas and small bowel transplant patients and donors.

RESEARCH PROJECTS

PROJECT TITLE: Organ Transplant Registry
RAC# 2121 012

PRINCIPAL INVESTIGATOR: *Broering D, MD, PHD, FEBS*
CO-INVESTIGATORS: *Alsebayel M, Alahmadi I, Nizami, I, Fayyad A*

OVERVIEW/AIM:

1. To analyze and interpret data on incidence, prevalence and patterns of transplant cases and other related activities initially at KFSH&RC and later regionally.
2. To measure the magnitude of end-stage diseases requiring organ transplantation primarily in Saudi Arabia and neighboring countries.
3. To identify actual and potential need for organ transplantation in Saudi Arabia.
4. To identify the different therapeutic and diagnostic procedures.

STATUS: Ongoing. Data collection, data entry and automatic reports development phase

1. Lung Transplant section of the registry application is completed, tested, consented and data collected for 6 case report forms.
2. Kidney Transplant section of the registry application is completed, tested, consented and data collected for 58 case report forms.
3. Liver Transplant section of the registry application is completed, tested, consented and data collected for 28 case report forms.
4. The database development is completed.
5. Started data entry for liver, lung, kidney transplant patients and living donors.

DEPARTMENT OF KIDNEY AND PANCREAS TRANSPLANTATION

PROJECT TITLE: Tuberculosis Post-Solid Organ Transplantation, Single Center Retrospective Study
RAC# 2121 074

PRINCIPAL INVESTIGATOR: *Alrajhi A, MD*
CO-INVESTIGATORS: Aleid H

OVERVIEW/AIMS: To study the incidence of tuberculosis in solid organ transplantation and outcomes of effective patients.

STATUS: Completed, Publication Phase (submitted to journal).

PROJECT TITLE: A Study of the Pathogenic Role of HCV Infection in the Development of Post Renal Transplant Diabetes Mellitus
RAC# 2071 013

PRINCIPAL INVESTIGATOR: *Aleid H, MD*
CO-INVESTIGATORS: *Ali T, Abdulbaki A*

OVERVIEW/AIM: To investigate diabetes mellitus post kidney transplant, analysis of respective and development of predictive model diabetes mellitus.

STATUS: Completed, Publication Phase (submitted to journal).

PROJECT TITLE: Acute Kidney Injury in Donors: Recipient's Outcomes
RAC# 2131 014

PRINCIPAL INVESTIGATOR: *Ali T, MD*
CO-INVESTIGATORS: *Aleid H, Almeshari K*

OVERVIEW/AIM: To determine the outcome of recipients receiving kidneys from donors with severe AKI.

PROJECT DESCRIPTION: A significant number of kidneys are discarded due to raised terminal serum creatinine of the donor. This study should encourage the health care professionals to accept such kidneys which will help in expanding the donor pool.

STATUS: Completed, Accepted for publication in QJM (Oxford Journal) DOI:http://dx.doi.org/10.1093/qjmed/hcv033803-811, First published online: 5 February 2015.

PROJECT TITLE: Retrospective Study to Distinguish the Incidence & Risk Factors of Post-Transplant Diabetes Mellitus
RAC# 2131051

PRINCIPAL INVESTIGATOR: *Aleid H, MD*
CO-INVESTIGATORS: *Ali T*

OVERVIEW/AIM: To develop and validate predictive model for diabetes mellitus post-kidney transplantation.

STATUS: Publication Phase (submitted to journal).

PROJECT TITLE: Comparative Study of Attitudes to Organ Donation in Two Arabic Speaking Communities
RAC# 2141 069

PRINCIPAL INVESTIGATOR: *Aleid H, MD*
CO-INVESTIGATORS: *Alyami A*

OVERVIEW/AIM: To investigate and compare the attitude of 2 Arabic speaking communities towards disease organ donation.

STATUS: Ongoing.

PROJECT TITLE: Ramadan Fasting in Kidney Transplant Recipients: A Single Center Retrospective Study
RAC# 2151104

PRINCIPAL INVESTIGATOR: *Ibrahim I, MD; Aleid H, MD*
CO-INVESTIGATORS: *Abdulbaki A, Shah Y, Eleid H, Elgamal H, Hammad E, Bazerbachi B*

OVERVIEW/AIM: To investigate and compare the outcome of patient who fast during month of Ramadan to the patient who did not fast.

STATUS: Ongoing.

PROJECT TITLE: Potential Kidney Donors with Asymptomatic Microscopic Hematuria: Histopathological Findings & Outcome
RAC# 2151079

PRINCIPAL INVESTIGATOR: *Hammad E, MD; Aleid H, MD*
CO-INVESTIGATORS: *Abdulbaki A, Shah Y, Elgamal H, Ibrahim I*

OVERVIEW/AIM: Overall aim is to conduct a retrospective study of donors with history of positive dipstick hematuria and isolated microscopic red blood cells in urine to assess the role of native kidney biopsy is clearance of these donors and accepting them as kidney donors.

SPECIFIC AIM:

1. To assess the short term graft survival of their potential recipients.
2. Describe the biopsy findings and diagnosis.
3. Short term follow-up of donors with Microscopic Hemataria post kidney donation.

STATUS: Ongoing. Final review before publication.

PROJECT TITLE: Dialysis access for Patient with Failing Kidney Transplantation
RAC# 2131 090

PRINCIPAL INVESTIGATOR: *AlHaq N, MD*
CO-INVESTIGATORS: *Aleid H*

OVERVIEW/AIM: To investigate the percentage of patient dialysis access with failing kidney transplantation.

STATUS: Submitted for publication to AJKD

PROJECT TITLE: Blood Group Incompatible Kidney Transplants: A Retrospective Study
RAC# 2151 190

PRINCIPAL INVESTIGATOR: *Ali T, MD*
CO-INVESTIGATORS: *Aleid H, Shah Y, Abdulbaki A, Almeshari K, Alahmadi I, Elgamal H, Bazerbachi B*

OVERVIEW/AIM: We aim to determine patient and graft survival of the recipients who received kidneys from ABOi donors.

PROJECT DESCRIPTION: Our group has published the experience of HLAi and ABOi transplantation in 2013. However, only 32 ABOi patients were included in the study and we reported only of the short-term outcomes. In this study, we aim to determine the short- and the long-term outcomes of ABOi kidney transplantation in this single center study.

STATUS: Ongoing.

PROJECT TITLE: Outcome of Renal Allograft Recipient with BKV Nephropathy
RAC# 2151 203

PRINCIPAL INVESTIGATOR: *Shah Y, MD; Khan A, MD*
CO-INVESTIGATORS: *Abdulbaki A, Ali T, Eleid H, Elgamal H, Ibrahim I, Hammad E, Bazerbachi B*

OVERVIEW/AIM: We aim to investigate the kidney allograft and patients' outcome who are diagnosed with BK polyomavirus (BKV) nephropathy on kidney allograft biopsy.

PROJECT DESCRIPTION: Kidney allograft and patient outcome with BKV nephropthy seems to be quite poor despite recent advancement in BKV diagnosis and its management. Short and long term outcome of such patients in our transplant population at KFSH&RC is not known, hence the need for this study.

STATUS: Ongoing.

DEPARTMENT OF LIVER AND SMALL BOWEL TRANSPLANTATION & HEPATOBILIARY PANCREATIC SURGERY

PROJECT TITLE: Liver Transplantation for HBV: Decreasing Indication & Changing Trends
RAC# 2151 023

PRINCIPAL INVESTIGATOR: *Al Hamoudi W, MD*
CO-INVESTIGATORS: *Elsiesy H, Bendahmash A, Al-Masri N, Ali S, Allam N, Al Sofayan M, Al Bahili H, Al Sebayel M, Broering D, Saab S, Aba Alkhail F*

STATUS: On-going, a progress report by 17 January 2016.

PROJECT TITLE: Small Case Series of Graft Versus Host Disease after Liver Transplantation: Single Center Experience
RAC# 2151 014

PRINCIPAL INVESTIGATOR: *Elsiesy H, MD*
CO-INVESTIGATORS: *Al Hamoudi W, Al Sebayel M, Broering D, Aba Alkhail F*

STATUS: Ongoing, a progress report by 28 March 2016

PROJECT TITLE: Therapeutic Drug Monitoring & Clinical Pharmacokinetics of Tacrolimus in Liver Transplant Recipients in Riyadh
RAC# 2151 175

PRINCIPAL INVESTIGATOR: *Elsiesy H, MD*
CO-INVESTIGATORS: *Qaddour E, Al Sebayel M, Ajlan A, Abou Auda H*

STATUS: Ongoing, A progress report by 25 September 2016.

PROJECT TITLE: Rabies Outbreak Involving Four Transplant Recipients in Kuwait and Saudi Arabia
RAC# 2150 340

PRINCIPAL INVESTIGATOR: *Elsiesy H, MD*
CO-INVESTIGATORS: *Hussain I, Aba Alkhail F, Elbeshbeshy H, Alhamoudi W, Al Sebayel M, Broering D, et.al*

STATUS: Ongoing, a progress report.

PROJECT TITLE: Redefining the Upper Limit of Normal of Alanin Transaminase (ALT) In Healthy Saudi Population
RAC# 2121 165

PRINCIPAL INVESTIGATOR: *Abalkhail F, MD*
CO-INVESTIGATORS: *Alsebayel M, Broering D, Albahili H, Alhamoudi W*

STATUS: Ongoing.

PROJECT TITLE: Biomarkers of operational tolerance after liver transplantation
RAC# 2130 029

PRINCIPAL INVESTIGATOR: *Burdelski M, MD, PHD*
CO-INVESTIGATORS: *Meyer B, Shagrani M, Broering D, Elsiesy H, Tayeb H, Boehnery M, Burkholder J, Woodman R, Algoufi T, Alyami H, Swerky W, Alhussaini H, Faiyad A*

OVERVIEW/AIM:

1. To collect biological samples from donors (single collection pre transplant) and recipients (pre-and post- transplant at regular intervals) for storage and analysis
2. To perform genetic screening of HLA locus and pharmacologically relevant genes of recipients and donors.
3. To undertake pharmacokinetic studies in recipient's pre-and post-transplant at regular intervals.
4. To conduct relevant cytokines measurements at regular intervals in recipient's pre- and post-transplant.
5. To study immunological phenotypes of circulating immune cells in recipient's pre- and post-transplants at regular intervals.
6. To conduct gene expression analyses in subpopulations of circulatory immune cells of recipient's pre- and post-transplants at regular intervals.
7. Measurement of circulating nucleic acids as indicators of non-tolerance.

PROJECT DESCRIPTION: The project includes a diverse set of parameters to indicate or exclude tolerance in liver transplant patients with the Organ Transplant Center. We will investigate immunological and genetic factors that affect clinical outcome. This will include pharmacogenetic, immunogenetic, immunological, biological, proteomic and genomic studies, before and after transplantation in the donor and host as appropriate. This will be both a prospective and retrospective study of liver transplant undertaken by the OTC at KFSH&RC.

STATUS: Ongoing, Case Enrollment, Data Collection and Data Compilation.

1. Informed consent obtained from 89 donors, labs collected and stored in research center.
2. Investigator meetings were held to continue managing the logistics of project and finalizing schedule for recipients labs, to be drawn.

PROJECT TITLE: Transarterial Radioembolization versus Chemoembolization for the Treatment of Advanced Hepatocellular Carcinoma; a Randomized Controlled Trial
RAC# 2131 134

PRINCIPAL INVESTIGATOR: *Al Sebayel M, MD*
CO-INVESTIGATORS: *Alsuhaibani H, Abaalkhail F, Elsiesy H, Hashim A, Hegab B, Jubran A, Alzahrani A, Bazarbashi S, Elsaadany A, Tuli M*

STATUS: Ongoing.

PROJECT TITLE: The impact of Donor and Recipient IL28B Polymorphisms on Hepatitis C virus Genotype for Liver Graft Re-infection and Outcome of Anti-viral Therapy on the Recurrent Infection Post-liver Transplant
RAC# 2131 135

PRINCIPAL INVESTIGATOR: *Aba Alkhail F, MD*
CO-INVESTIGATORS: *Alsebayel M, Elsiesy H*

STATUS: Ongoing.

PROJECT TITLE: Spontaneous Clearance of Hepatitis C Infection After Liver Retransplantation
RAC# 2141 051

PRINCIPAL INVESTIGATOR: *Elsiesy H, MD*
CO-INVESTIGATORS: *Almoutaz H, Al Sebayel M, Zakareya T, Mohamed H, Abaalkhail F*

STATUS: Ongoing.

PROJECT TITLE: Rescue Therapy of Retrieved Organs from Deceased Donors: Liver *Ex vivo* Machine Perfusion
RAC# 2141 055

PRINCIPAL INVESTIGATOR: *Al Sebayel M, MD*
CO-INVESTIGATORS: *Boehnert M, Albahili H, Alsheikh Y, Elsayed R, Almohanna F*

STATUS: Ongoing.

PROJECT TITLE: The Correlates of Sexual Dysfunction in Liver Transplantation Patients and the Impact of Management
RAC# 2091 016

PRINCIPAL INVESTIGATOR: *Al Sebayel M, MD*
CO-INVESTIGATORS: *Elsiesy H, Albahili H*

STATUS: Ongoing.

PROJECT TITLE: A 24-month, Randomized, Controlled, Study to Evaluate the Efficacy and Safety of Concentration-Controlled Everolimus Plus Reduced Tacrolimus Compared to Standard Tacrolimus in Recipients of Living Donor Liver Transplants
RAC# 2141 052

PRINCIPAL INVESTIGATOR: *Broering D, MD, PHD, FEBS*
CO-INVESTIGATORS: *Boehnert M, Elsiesy H, Alhussaini H, Alsuhaibani H, Alkortas D, Moslmani R, Gaber E, Bazerbachi B, Hervera K*

OVERVIEW/AIMS:

Primary Objectives:

1. To demonstrate comparable efficacy as measured by the composite efficacy failure of treated biopsy proven acute rejection (tBPAR), graft loss (GL) or death (D) with everolimus in combination with reduced tacrolimus compared to standard exposure tacrolimus, at 12 months post-transplantation, in living donor liver transplant recipients.
2. To demonstrate at least comparable renal function, measured by change in estimated GFR from randomization to Month 12 post-transplantation, with everolimus in combination with reduced tacrolimus, compared to

standard exposure tacrolimus, in living donor liver transplant recipients.

STATUS: Ongoing, data collection and data entry.

1. Patient 001 withdrew his consent after screening and before transplantation.
2. Patient 002 was enrolled in the study but was screen failure because subject was discontinued in the study medication due to Exclusion Criteria No. 26 were the subject was still on IV antibiotics due to systemic infection on week 5 of randomization. Subject will still be followed up as per Protocol Section 5.5.9.1.
3. Patient 003 was also enrolled in the study and initial adverse event (which was not related to the study medication) was reported to Novartis Adverse Events and ORA. Patient died on 13 July 2015, a follow up adverse event was also reported (not related to study medication) to Novartis Adverse Events and ORA.
4. Patient 004 was enrolled in the studyas well, IRT call was done for screening phase but unfortunately the transplant was delayed. Patient was transplanted a month later. Patient stopped receiving Tacrolimus and was switched to cyclosplorine due to Tacrolimus Toxicity and another IRT call was entered for screen failure.
5. Patient 005 withrew his consent after screening and before randomization.
6. Patient 006 was randomized after transplantation to Everolimus plus Reduced Tacrolimus arm and is being followed up as per protocol.
7. Patient 007 withrew his consent after transplantation and before randomization.
8. Patient 008 was randomized after transplantation to Everolimus plus Reduced Tacrolimus arm and is being followed up as per protocol.

OTC-ORGAN TRANSPLANT RESEARCH SECTION

PROJECT TITLE: Role of T Regulatory Cells (Tregs) in Inducing Immune Tolerance in Mouse Model of Trachea Transplantation
RAC# 2140 036

PRINCIPAL INVESTIGATOR: *Khan MA*
CO-INVESTIGATORS: *Broering D*

OVERVIEW/AIM: Organ transplantation is recognized as the most effective therapy for patients with end-stage acute and chronic organ failures which include heart, lung and liver transplantations. Despite remarkable short-term graft and patient survival, organ survival in most of organ transplantations continues to face several major challenges, including modest long-term graft survival due to chronic rejection and critical side effects of long-term immunosuppressive therapy (which is required for the prevention of allograft rejection). Allograft rejection is a major barrier to the success of most organ transplantations. To prevent allograft rejection, transplant recipients require long-term immunosuppression, which is associated with increased susceptibility to infection, increased risk of malignancy, and increased morbidity and mortality. Several types of T cells with immunosuppressive properties have been identified, but FOXP3+ regulatory T (Treg) cells have emerged as a dominant cell type; they are critically involved in the induction and maintenance of immune tolerance to alloantigens. A major goal of this proposed project, therefore, is the induction of tolerance, to enable indefinite allograft survival with minimal /or without the need for life-long immunosuppression.

T regulatory cells contribute to induce tolerance. This will determine whether infusion of Tregs in recipients results in reduced graft hypoxia,

improved graft perfusion/oxygenation and less airway remodeling.

PROJECT DESCRIPTION: The major goal of this proposal is to further study the role of immune cell, especially Tregs, in inducing tolerance in allografts which facilitate microvascular flow and induce tissue oxygenation for the survival of allografts. Previous literature and some of our published findings on CD4+ and CD8+ T cell subpopulation (4) encourage us to further study this unique subset (Treg) as a major T cell subset in inducing immunological tolerance in mouse model of trachea transplantation. Experiments are designed to determine if Tregs cell are sufficient to induce tolerance, and preserve microvasculature and ultimately, rescue rejecting allografts without the need of required immunosuppression.

STATUS: Data collection and analysis.

PROJECT TITLE: Role of Complement Factor C5a and Surfactant Protein-D in Preserving Microvasculature in Rejecting Allografts
RAC# 2150 017

PRINCIPAL INVESTIGATOR: *Khan MA*
CO-INVESTIGATORS: *Broering DC, Vater A, Bhatia UK*

OVERVIEW/AIM: Loss of microvasculature may be an unappreciated root cause of chronic rejection, which is manifested by fibrosis in all solid organ transplants (4,6). The complement system is an innate immune effector mechanism with the ability to recognize non-self (pathogens, foreign antigens etc), altered self (aggregated proteins, apoptotic and necrotic cells) and transformed self (cancer cells) and initiate local inflammatory responses (1,6) that eliminates pathogens and recruit cellular repair mechanisms. The complement activation, which involves a conglomeration of a number of soluble proenzymes, membrane-bound and soluble regulators can take place via three pathways – classical, alternative, and lectin pathways. All three complement activation pathways converge in the formation of C5 convertase (C4b2a3b in the classical and lectin pathway, C3bBb3b in the alternative pathway), which cleaves C5 to C5a and C5b. C5a has potent anaphylatoxin activity and is chemotactic, while C5b functions with its hydrophobic binding site as an anchor on the target cell surface to which the lytic membrane attack complex (MAC) forms. Complement-mediated injury of the vascular endothelium has been reported to be a hallmark of rejecting xenografts (2); microvessel damage in this setting leads to vascular leakiness, microvascular congestion, thrombus formation, pulmonary edema and neutrophilic invasion of the microvasculature (2). The complement system is a potent activator of initiating and amplifying tissue inflammation, which is further mediated through active complement fragments, anaphylatoxins, generated through different activation pathway. Anaphylatoxins are the best characterized proteolytic fragments, which include C3a, C4a and C5a. C5a is exceptionally powerful in stimulating neutrophil chemotaxis, adherence, respiratory burst, generation and degranulation. C5a also stimulates neutrophils and endothelial cells to present more adhesion molecules and local release of C5a at sites of inflammation results in powerful pro-inflammatory stimuli in acute and chronic conditions, such as immune complex associated diseases in general asthma (7); systemic inflammatory response syndrome; acute respiratory distress syndrome; inflammatory bowel syndrome (10);reperfusion injury of organs such as heart (9), lung, liver, kidney (8). Of note, although cleavage of C5 leads to C5a as well as the MAC, the clinical characteristics of C5 deficiency do not differ significantly from those of other terminal component deficiencies (e.g. C6,

C7, C8, C9) suggesting that the absence of C5a does not contribute significantly to the clinical status in C5-deficient conditions. Therefore, the targeted inhibition of C5a secures to be the ideal control, so that the normal up- and downstream disease- preventing functions of complement remain unaffected. Thus, targeted inhibition only blocks the deleterious over production of the pro-inflammatory anaphylatoxin. Numerous inhibitors to C5 or C5R have been successfully tested in *in vivo* models, and further in clinical trials.

The global hypothesis to be tested in this project is that allograft microvasculature is rendered susceptible to antibody-dependent classical pathway activation, allogenic CD4+ T cells and C5a generation, and specific blocking of both C5/C5a along with anti-inflammatory effects of Tregs will rescue allograft through microvascular reestablishment.

PROJECT DESCRIPTION: In the current research proposal, we will investigate the targeted therapeutic roles of NOX-D21 a specific inhibitor of C5/C5a of complement system in dampening the inflammation and tissue fibrotic remodeling during allograft rejection and synergistic effects of Treg cells in experimental mouse model of OTT (3). Therefore, the key objective of this proposed research is to demonstrate that therapeutic administration of NOX-D21 (a C5/C5a inhibitor) may facilitate long-term survival of allografts by preserving microvascular flow and prevent fibrosis. We have developed a technique of airway transplantation, which resembles the airway fibrosis seen in clinical lung transplantation. In the OTT model, the mice easily breathe through the transplants even when they are becoming scarred. We will carefully examine how C5a inhibition mediated immune suppression affect the small blood vessels in these rejecting transplants and how the health of the blood vessels correlates with the health of the rejecting transplants. Results from these studies will help devise new therapies for transplant patients. In summary, we will investigate the specific role of complement C5a inhibitor using the C5a antagonist NOX-D21 (from NOXXON Pharma, Germany), which is functionally an improved follow-up compound of the previously studied C5a antagonist NOX-D19, in dampening complement-mediated inflammation cascade during allograft rejection in experimental mouse model of OTT (3). NOX-D19 had shown improved vascular integrity when administered to C3-knock-out mice (5). Furthermore, we will test the therapeutic potential of NOX-D21 for the allograft health with Tregs, a well-established anti-inflammatory molecule, and how this combination therapy may rescue allograft tracheal transplants for long term survival.

STATUS: Data collection and analysis.

PUBLICATIONS – ORIGINAL ARTICLES

DEPARTMENT OF LIVER AND SMALL BOWEL TRANSPLANTATION & HEPATOBILIARY PANCREATIC SURGERY

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- Al Sebayel M, Elsiesy H. "Organ Donor Allocation System for Liver Transplantation in the Kingdom of Saudi Arabia: Call for Major Revision." *Saudi J Gastroenterol*. 2015 Sep-Oct;21(5):267-8.
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ORAL PRESENTATIONS

DEPARTMENT OF KIDNEY AND PANCREAS TRANSPLANTATION

- Aleid H, Ali T. "Predictive Model of Diabetes Mellitus after Kidney transplantation." European Society of Organ Transplantation, 13–16 September 2015, Brussels, Belgium.
- Aleid H, Mukhaini S, Alrajhi A. "Mycobacterium Tuberculosis in Solid Organ Transplantation, Impact of Expanded Isoniazid Prophylaxis." European Society of Organ Transplantation, 13–16 September 2015, Brussels, Belgium.
- Hammad E, Ali T, Aleid H. "Potential Kidney Donors with Asymptomatic Microscopic Hematuria: Histopathological Findings & Outcome." European Society of Organ Transplantation, 13–16 September 2015, Brussels, Belgium.
- U Haq N, Aleid H. "Vascular Access Types in Patients starting Hemodialysis with Failed Kidney Transplants; A Retrospective Analysis." 9th Congress of Vascular Access Society, 15–18 April 2015, Barcelona, Spain.

DEPARTMENT OF LIVER AND SMALL BOWEL TRANSPLANTATION & HEPATOBILIARY PANCREATIC SURGERY

- AlShagrani M. "Progressive Familial Intrahepatic Cholestasis - Experience from KSA." Fetal Medicine, Paediatrics, Paediatric Gastroenterology, Hepatology and Nutrition, 26–28 February 2015, Abu Dhabi, UAE.
- Elsiesy H. "Graft Versus Host disease after Liver Transplantation: Single Center Case Series." APASL 2015; 12–15 March 2015, Istanbul, Turkey.

- Broering D, Fayyad A, Shagrani M, AlGoufi T, ElSheikh Y, Elgohary A, Burdelski M. "Evolution of Pediatric Liver Transplantation in a High Volume Saudi Organ Transplant Center." 8th Congress on Pediatric Transplantation, 28–31 March 2015, San Francisco, CA, USA.
- Broering DC. "Minimally Invasive Living Donor Hepatectomy for Pediatric Recipients: Technique and Results." EAHPBA 11th International Congress, 21–24 April 2015, Manchester, UK.
- Broering DC. "Split Liver Transplantation for Two Adults." 21st Annual International Congress of ILTS, 08–11 July 2015, Sheraton Chicago Hotel & Towers, Chicago, IL, USA.
- Hegab B, Boehnert M, Elgohary A, Elsheikh Y, Saleh Y, Al Abbad S, Al Bahili H, Al Sebayel M, Broering D. "Intra-operative Hepatic flow measurement in Living Donor Liver Transplantation: Does it really affect inflow modulation during Transplantation?" Congress of the Asian Society of Transplantation, 23–26 August 2015, Singapore.
- Hegab B. "Intra-operative Hepatic flow measurement in Living Donor Liver Transplantation: Does it really affect inflow modulation during Transplantation?" 17th Congress of the European Society for Organ Transplantation, 13–16 September 2015, Brussels, Belgium.
- Elsiesy H, Aba Alkhail F, Al Hamoudi W, Alsuhaibani H, Al Sebayel M, Broering D, Shagrani M. "Plasmapharesis, Intravenous, Immunoglobulin and Rituximab Successfully Treat Recurrent progressive Familial Intrahepatic Cholestasis Type 2 after Liver Transplantation." ESOT, 13–16 September 2015, Brussels, Belgium.
- Shagrani M, Burdelski M, Al Sebayel M, Zahr EF, Elsheikh Y, Albahili H, Alhussaini H, Algoufi T, Broering D. "ABO- Incompatible liver Transplantation in Children, Role of HLA- Single Centre Experience." ESOT, 13–16 September 2015, Brussels, Belgium.
- Broering DC. "Post-Transplant Ascites: Is it HVOTO, Hyper perfusion or just small for size?" Center for Liver and Biliary Sciences (CLBS) Symposium, 25–27 September 2015, New Delhi, India.
- Broering DC. "Strategies to Optimize Outcome of Living Donor Liver Transplantation." 6th PALTS (Pan Arab Liver Transplant Society) Congress, 15–16 October 2015, Cairo, Egypt.
- Al Sebayel M. "Organ Donor Allocation System for Liver Transplantation in the Kingdom of Saudi Arabia: Call for Major Revision." 2015 Organ Donation Congress, 17–20 October 2015, Seoul, South Korea.

OTC-ORGAN TRANSPLANT RESEARCH SECTION

- Khan MA. "CD4+ T cells and complement independently mediate graft ischemia in the rejection of mouse OTTs." KFSH&RC, Riyadh, KSA.
- Khan MA. "Immuno suppressive (Treg) Therapy in Transplantation: Bench-to-Bedside program." KFSH&RC, Riyadh, KSA.
- Khan MA. "Treg Cell-Based immunotherapy: The Next Pillar of Medicine." KFSH&RC, Riyadh, KSA.

POSTER PRESENTATIONS

OTC-DEPARTMENT OF KIDNEY AND PANCREAS TRANSPLANTATION

- Brockmann J. "Pancreas Transplant." Congress of the Asian Society of Transplantation (CAST), Singapore, 23–26 August 2015.
- Almojalli H. "Incidence of Urinary Tract Infection (UTI), Hydronephrosis and Their Effect on Glomerular Filtration Rate (GFR) At One Year Post Kidney Transplant on Children." RAC#

213 1006 in ESOT, September 2015, Brussels, Belgium.

OTC-DEPARTMENT OF LIVER AND SMALL BOWEL TRANSPLANTATION & HEPATOBILIARY PANCREATIC SURGERY

- Abdoh Q, Alhussaini H, Almansour M, Elsiesy H. "Aggressive Recurrence of Primary Hepatic Epithelioid Haemangioendothelioma (HEHE) after liver Transplantation." APASL 2015; 12–15 March 2015, Istanbul, Turkey.
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- AlShagrani M. "Association between fibrocystic Liver kidney disease and HCC-Case Report." IPTA 8th Congress 2015, 28–31 March 2015, California, USA.
- AlShagrani M. "Role of HLA at ABO-I liver Transplantation in Children." IPTA 8th Congress 2015, 28–31 March 2015, California, USA.
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- Aba Alkhail F, AlSebayel M, Broering D, Alhamoudi W, Shagrani M, Yousif S, Alhussaini H, Elsiesy H, Alquaiz M. "Liver Transplantation for Progressive Familial Intrahepatic Cholestasis Type 3(PFIC-3) presenting in the 5th decade of Life." EASL 50th: The International Liver Congress 2015, 22–26 April 2015, Vienna Austria.
- Elsiesy H, Abaalkhail F, Alhamoudi W, Alhussaini H, Alsebayel M, Broering D, Shagrani M. "Plasmapharesis, Intravenous immunoglobulin and Rituximab successfully treat recurrent Progressive Familial Intrahepatic Cholestasis type 2 (PFIC-2) after Liver transplantation." American Transplant Congress, 02–06 May 2015, Philadelphia, PA, USA.
- Elsiesy H. "Plasmapharesis, Intravenous, Immunoglobulin and Rituximab Successfully Treat Recurrent Progressive Familial Intrahepatic Cholestasis Type 2 after Liver Transplantation." ILTS 2015; 08–11 July 2015, Chicago Illinois, USA.
- Elsiesy H, Aba Alkhail F, Alhamoudi W, Alsuhaibani H, Al Sebayel M, Broering D, Shagrani M. "Gilbert's syndrome as a cause of unconjugated hyperbilirubinemia after Living donor Liver transplantation." ILTS 2015; 08–11 July 2015, Chicago Illinois, USA.
- Elsiesy H. "Living Donor Liver Transplant using Donors with Gilbert Syndrome." ILTS 2015; 08–11 July 2015, Chicago Illinois, USA.
- Broering D. "Minimally Invasive Living Donor Hepatectomy for Pediatric Recipients: Technique and Results." ILTS21st Annual International Congress, 08–11 July 2015, Chicago, IL, USA.
- Hegab B, Boehnert MU, Elgohary A, El-Sheikh Y, Saleh Y, Alabbad S, Al Bahili H, Al-Sebayel M, Broering D. "Intra-operative hepatic flow measurement in living donor liver

transplantation: Does it really affect inflow modulation during transplantation?" ILTS 21st Annual International Congress, 08–11 July 2015, Chicago, IL, USA.
- Hegab B. "The Usefulness of Laparoscopic Hernia Repair in the Management of Incisional Hernia Following Liver Transplantation" CAST 2015, Congress of the Asian Society of Transplantation, 23–26 August 2015, Singapore.
- Shagrani M, Kumar K, Alkhail F, Alsebayel M, Alhussaini H, Alquaiz M, Broering D, Elsiesy H. "Liver Transplantation for Progressive Familial Intrahepatic Cholestasis Type 3(PFIC-3) presenting in the 5th decade of Life" ESOT, 13–16 September 2015, Brussels, Belgium.
- Broering D, Fayyad A. "Organ Transplant Registry: A Clinical and Research Tool? Or a Key to Operational Effectiveness of a Large Multi-Organ Transplant Center in the Middle East!" ESOT 2015, 13–16 September 2015, Brussels, Belgium.
- Elsiesy H. "Rabies Outbreak Involving Four Transplant Recipients." 15th Annual Surgical Research Day, 26 November 2015, PGC KFSH&RC, Riyadh, KSA.

PRESENTATIONS – INVITED SPEAKERS

OTC-DEPARTMENT OF KIDNEY AND PANCREAS TRANSPLANTATION

- Aleid H. "Expanding the pool of kidney donor." International Conference of Nephrology, 09–11 April 2015, Al-Hassan, KSA.
- Aleid H. "Integrating the Immunological and clinical data for kidney transplantation." International Symposium on Histocompatibility and Transplantation, 28–29 October 2015, Riyadh, KSA.

OTC-DEPARTMENT OF LIVER AND SMALL BOWEL TRANSPLANTATION & HEPATOBILIARY PANCREATIC SURGERY

- Elsiesy H. "HCC Management Strategy." 2015 Radiation in Medicine Symposium & Workshop, 24–26 February 2015, Riyadh, KSA.
- Elsiesy H. "Hepatitis C in local Views." 27–28 March 2015, 2nd Gulf Liver Summit, Dubai, UAE.
- Boehnert M. "Ex-Vivo Liver Machine Perfusion-Storage, Assessment and Repair of Marginal Graft." 3rd International Meeting of Hepato-Pancreato-Biliary Liver Transplant Surgery, 01–03 April 2015, Anaesthesia and Intensive Care Department, National Liver Institute, Menofia University, Cairo Egypt.
- Hegab B. "Intra-operative hepatic flow measurement in living donor liver transplantation: Does it really affect inflow modulation during transplantation?" 3rd International Meeting of Hepato-Pancreato-Biliary Liver Transplant Surgery, 01–03 April 2015, Anaesthesia and Intensive Care Department, National Liver institute, Menofia University, Cairo Egypt.
- Al Bahili H. "Advance Liver Surgery", Scientific Congress of Saudi General Surgical Society (SGSS), 07–09 April 2015, Taif, Saudi Arabia.
- Elsiesy H. "Optimizing patient pre-liver transplant" Saudi Critical Care Society, 21–23 April 2015, Al Faisaliah Hotel, Riyadh, KSA.
- Shagrani M. "Progress and outcome of the first high-volume pediatric liver Transplantation program in Saudi Arabia." Elite Ped. GI Congress, 27–29 May 2015, Dubai, UAE.
- Elsiesy H. "Liver Cirrhosis Leading to Pulmonary Disease" Department of Medicine, Thursday Case Presentation, 07 May 2015, KFSH&RC-Riyadh, KSA.
- Al Sebayel M. (Committee Member), 2nd HCC Monothematic Symposium, 30 May 2015, Intercontinental Hotel, Jeddah, KSA.

- Aba Alkhail F. 22nd Internal Medicine Board Review Course PART II, 05–10 September 2015, Postgraduate Auditorium Centre, KFSH&RC.
- Broering DC. ESOT – 5th European Liver and Intestine Split Liver Course. Accredited by the UEMS Section of Transplantation Surgery Accreditation Number: 12738. Session 2: Technical Aspects – Donor, Speaker, "Full-Left / Full-Right Split-Liver Procedures." Master, Practical Course Session. University Hospital, Ghent Faculty of Medicine, 11–12 September 2015, Ghent, Belgium.
- Shagrani M. "Antibody and B-Cell depletion free ABO incompatible (ABOi) pediatric liver transplantation." "International Symposium on Histocompatibility & Transplantation", 28–29 October 2015, Postgraduate Center Auditorium, KFSH&RC, Riyadh, KSA.
- Elsiesy H. "Management of Multiple Liver Masses." 05 November 2015, Department of Medicine, Thursday Case Presentation, KFSH&RC-Riyadh, KSA.
- Aba Alkhail F. 24 November 2015, University of Dammam, KSA.
- Aba Alkhail F. "Acute HCV in HIV & Management of Coinfection." 12th Annual AIDS Symposium: Stepping up the place, 27-29 November 2015, Park Hyatt- Jeddah, KSA.
- Aba Alkhail F. "Cure Don't Compromise" Harvoni Launch Event, 05 December 2015. Movenpick Hotel, Riyadh, KSA.

OTC-SECTION OF LUNG TRANSPLANTATION

- Nizami IY. "A new breath. A new life." Multidisciplinary Conference, 08 January 2015, Sultan Qaboos University, Musqat, Oman.
- Nizami IY. "Lung Transplant Overview." Grand Rounds, 08 January 2015, Royal Hospital, Musqat, Oman.
- Nizami IY. "ECMO in lung transplant." Cardiac Center Grand Rounds, 19 March 2015, KFSH&RC, Riyadh, KSA.
- Nizami IY. "Adult Cystic Fibrosis Care at KFSH&RC." Cystic Fibrosis Conference and Cystic Fibrosis Awareness Day, 04 November 2015, KFSH&RC, Riyadh, KSA.

OTC-ORGAN TRANSPLANT RESEARCH SECTION

- Optimization of mouse model of trachea transplantation.
- Optimization of T regulatory cell isolation.
- Optimization of tissue pO2 and blood flow monitoring in transplants.
- Tissue regeneration project: established portal vein ligation – induced liver regeneration model in rats and evaluated the effect of epoxyeicosanoid treatment in this model.
- Tissue engineering project: we have initiated projects involving stem cells culture and de- and re-cellularisation of organs including liver and kidney.
- Organ preservation and perfusion in small and large animal models.

APPROVED GRANTS / ONGOING KACST PROJECTS

- Broering D, Alsebayel M, Alahmadi I, Nizami I, Fayyad A. KACST 12-MED2418-20 "Organ Transplant Registry."
- Boehnert M. KACST 15-MED4713-20 "Mechanisms of Ischemic Type Biliary Strictures after Liver Transplantation of Marginal Grafts – Normothermic Ex Vivo Liver Perfusion (NEVLP) – Rat Model."
- Al Sebayel M, Alsuhaibani H, Abaalkhail F, Elsiesy H, Hashim A, Hegab B, Jubran A, Alzahrani A, Bazarbashi S, Elsaadany A, Tuli M. KACST 13-MED1506-20 "Transarterial Radioembolization versus Chemoembolization for the Treatment of Advanced Hepatocellular Carcinoma: A Randomized Controlled Trial."
- Alsebayel M, Albahili H, Broering D, Elsheikh Y, Abaalkhail F, Boehnert M. KACST 13-MED1503-20 "Rescue Therapy Of Retrieved Organs From Deceased Donors: Liver Ex Vivo Machine Perfusion (Sheep Model)."

DEPARTMENT OF
PEDIATRIC HEMATOLOGY / ONCOLOGY

PEDIATRIC HEMATOLOGY / ONCOLOGY

CHIRMAN

Amani Al-Kofide MD

MEMBERS

Hassan El Solh, MD
Ibrahim Al Fawaz, MD
Abdullah Al Jefri, MD
Mouhab Ayas, MD
Afshan Ali, MD
Abdulrahman Al-Musa, MD
Amal Al-Seraihy, MD
Ali Al- Ahmari, MD
Mahasen Saleh, MD
Suliemman Al-Swaidan, MD
Ibrahim Al Ghemlas, MD
Ashraf Radwan, MD
Hassan Shahin, MD
Samer Markiz, MD
Nicy Joseph, MD
Saba Parween Haque, MD
Ameer Nadeem, MD
Ghulam Pathan, MD
Roula Barmada, MD
Naeem Butt, MD
Amjad Abbas, MD
Mohammed Mustafa, MD
Muhammed Ameen, MD
Hasna Al Hamzi, MD
Basheer Iqbal, MD
Hana Al Juliah, MD
Khulood AlSayyad, MD
Ameera AlOraibi, MD
Nada Elsheikh, MD
Maha Al Mofareh, MD
Mona Al Asseri, MD
Amal Bin Hassan, MD
Murtada Al Sultan, MD
Khawar Siddiqui
Rafat Jafri
Saira Jarfi
Mary Grace Barria
Sohaib Zulfiqar
Anotenette G. Amao
Viqaruddin Mohammad Khaja
Majid Tiba
Amer Ahmed
Mohammad Al Qaissi
Marilou T Carido
Leah Abad
Rose Christine Lu
Soledad Turton
Epifania Pastor
Jerome Racacho
Reymond Arboleda
Mohammed Al Eid
Abdulaziz Al Obaidy

SECTIONS

1. Section of Leukemia / Lymphoma
2. Section of Solid Tumours
3. Section of Hematology
4. Section of Bone Marrow Transplant

The Department of Pediatric Hematology/ Oncology provides comprehensive care in children and adolescent with Leukemia, Brain Tumors, Lymphoma, Bone and other Solid Tumors, in addition to patients with malignancies, non-malignant hematological and bleeding disorders.

SECTION OF LEUKEMIA / LYMPHOMA

This service remains the premier referral point for patients with leukemia and lymphoma, particularly for patients with conditions which cannot be treated easily at other centers in the Kingdom. The service is staffed by specialists with years of experience in the management of childhood leukemia and lymphoma. Outcome based, state-of-the-art protocols developed here are utilized to guide the treatment of patients at several institutions in the Kingdom. Clinical research remains an integral component of the work.

SECTION OF BONE MARROW TRANSPLANT

The Section of Pediatric Stem Cell Transplant provides care for children in need of Stem Cell Transplantation. The program performs more than 130 stem cell transplants per year, for patients with various malignancies and non-malignant hematological disorders as well as for immune deficiency and metabolic diseases.

SECTION OF SOLID TUMOURS

The Solid Tumor service has 3 approved programs and coordinates the multidisciplinary treatment of Solid Tumors, Neuro-Oncology, and Histiocytosis.

SECTION OF HEMATOLOGY

The Section of Hematology has two approved programs; Hemophilia and Hemoglobinopathy. It handles several other blood disorders and cares for a large population of patients with Bone Marrow Failure especially Fanconi Pancytopenia Syndrome

CENTRAL DATA UNIT

The Central Data Unit's primary goal is to provide support for clinical research into childhood cancers and blood disorders by providing data management processing and analysis services to support research programs.

RESEARCH PROJECTS

PROJECT TITLE: Hematopoietic Stem Cell Transplantation in Children with Griscelli Syndrome: A Single-Center Experience
RAC# 2081044

PRINCIPAL INVESTIGATORS: *Ali Al-Ahmari, A. Al-Ghonaium*
CO-INVESTIGATORS: *M. Ayas, H. Al-Mousa, A. Al-Jefri, B. Al-Saud, A. Al-Seraihy, S. Al-Mohsen, M. Al-Mahr, H. Al-Dhekri, H. El-Solh*

PROJECT TITLE: The Outcome of Patients with HLH Treated with Immuno-Chemotherapy Followed by SCT: A Single Centre Experienc
RAC# 2081052

PRINCIPAL INVESTIGATOR: *Ali Al Ahmari*
CO-INVESTIGATORS: *Mouhab Ayas, Amal Seraihy, Al Jefri, Ibrahim Al Fawaz, Hassan El Solh, Mohammed Al Mahr*

PROJECT TITLE: Epidemiological, Clinical, Labaratory and Molicular Genetic Characterization of Childhood A.L.L. in The Mid East and their Correlation with Induction Toxicity and Outcome. A Prospective Multi-Insitute International Collaborative Study
RAC# 2081108

PRINCIPAL INVESTIGATORS: *Abdlh Al-Nasser, Asim Belgaumi*
CO-INVESTIGATORS: *Ali Al Ahmari, Mohammed Al Mahr, Hassan El Solh, Amal Al Seraihy, Abdulrahman Al Musa, Mahasen Saleh*

PROJECT TITLE: Determination of the Molecular Basis and Phenotype of Glanzmann Thrombasthenia in Saudi Arabian Patients
RAC# 2091067

PRINCIPAL INVESTIGATOR: *Abdulrahman Al-Musa*
CO-INVESTIGATORS: *Hassan Masmali, Abdulmajedd Albangan, Randa Al Nounor, Tarek Owaidah, Al Jefri, Mahasen Saleh, Hazza Al Zahrani, Rashed Naser, Mahmoud Abu Riash, Hala Aba Alkhail, Chaker Adra,Manogaran Subramanian*

PROJECT TITLE: International Pediatric Fungal Network Registry
RAC# 2091044

PRINCIPAL INVESTIGATOR: *Ibrahim Bin Hussain*
CO-INVESTIGATOR: *Asim Belgaumi*

PROJECT TITLE: Related Haploidentical T-cell Depleted Stem Cell Transplantation in Patients with Fanconi Anemia Lacking Matched Related Donors
RAC# 2101048

PRINCIPAL INVESTIGATORS: *Mouhab Ayas, Ashraf Radwan*
CO-INVESTIGATORS: *Al Jefri, Al Seraihy, Al Ahmari, Mohammed Mahr, Y. Khafaga, Adelmoneim Eldali, Morad Al Kaff,Samir Markiz, Hassan El Solh*

PROJECT TITLE: Acute Infant Leukemias; Clinical Characteristics and Outcomes
RAC# 2101046

PRINCIPAL INVESTIGATORS: *Amal Al-Seraihy, Ashraf Radwan*
CO-INVESTIGATORS: *Ali Al Ahmari, Mouhab Ayas, Ali Al Shehri, Tarek Owaidah, Asim Belgaumi*

PROJECT TITLE: Prevalence of CMMD Syndrome in Saudi Pediatric Acute Lymphoblastic Leukemia
RAC# 2120017

PRINCIPAL INVESTIGATOR: *Khawla Sami Al-Kuraya*
CO-INVESTIGATORS: *Asim Belgaumi, Hassan El Solh,Abdul Khalid Siraj, Azhar Hussain, Jehad Abubaker, Prashant Bavi, Shahab Uddin Khan*

PROJECT TITLE: Can Low Level Chimerism in Patients with Thalassemia Major After Allogeneic HSCT Effectively Leads to Independence from PRBC Transfusion
RAC# 2151138

PRINCIPAL INVESTIGATOR: *Mouhab Ayas*

PROJECT TITLE: Primary Immunodeficiency Disease Registry
RAC# 2081111

PRINCIPAL INVESTIGATORS: *Amal Al Seraihy, Bandar Al Saud*
CO-INVESTIGATOR: *Amal Al Seraihy*

PROJECT TITLE: Clinical Characteristics and Treatment Outcome of Childhood A.L.L. in Saudi Arabia: A Multi-Institutional Retrospective National Collaborative Study
RAC# 2091806

PRINCIPAL INVESTIGATOR: *Asim Belgaumi*
CO-INVESTIGATORS: *Reem Al-Sudairy, Abdullah Al Nasser, Ali Al Ahmari, Ibraheem Abosoudah, Reema Al-Hayek, Talal Al-Harbi, Fahad Al-Manjomi, Musa Al-Harbi, Hasna Al-Ghamdi Aldulrahman Alsultan, Mohammed Al-Shahrani*

PROJECT TITLE: Proteome Profile of Acute Myeloid Leukemia (AML) Patients In Saudi Arabia
RAC# 2130010

PRINCIPAL INVESTIGATORS: *Amer A Rahman Almaiman, Ayodele A Karim Alaiya*
CO-INVESTIGATORS: *Tareeq Owaidah, Asim Belgaumi, Walid Rasheed, Nasir Bakhshi, Mahmoud Aljurf*

PROJECT TITLE: Safety of Cyclophosphamide Infusion in the Outpatient Setting in Pediatric Patients with Malignancies. A Retrospective Review
RAC# 2131071

PRINCIPAL INVESTIGATOR: *Afshan Ali*
CO-INVESTIGATOR: *Amal Al Sabahi, Diana Bushnak*

PROJECT TITLE: Autoimmune Hemolytic Anemia In Children: Pattern of Clinical Presentation and Management Outcome in KFSH&RC: An Eight Years Experience
RAC# 2141097

PRINCIPAL INVESTIGATOR: *Mahasen Saleh*
CO-INVESTIGATOR: *Jumana El Eita*

PROJECT TITLE: Submission of Data on Pediatric Patients Undergoing Stem Cell Transplantation at KFSH&RC, Riyadh, KSA, to the Center of International Blood & Marrow Transplant Research (CIBMTR) and The European Society for Blood and Marrow Transplantation (EBMT) Databases
RAC# 2141033

PRINCIPAL INVESTIGATORS: *Mouhab Ayas, Amal Al-Seraihy*
CO-INVESTIGATORS: *Hassan El Solh, Ali Al-Ahmari, Abdullah Al-Jefri, Ashraf Radwan,Samer Markiz,Amal Mohammad, Viqaruddin M Kaja*

PROJECT TITLE: Epidemiological Trends of Disease and Outcome of Childhood Acute Lymphoblastic Leukemia in Saudi Arabia - A Long Term Evaluation Study
RAC# 2141133

PRINCIPAL INVESTIGATOR: *Suleimman Alsweedan*

CO-INVESTIGATORS: *Ali Al Ahmari, Amal Seraihy,Hassan El Solh, Hasan Shahin, Nicey Joseph, Naemah Farhan, Nasir Bakshi, Syed Rafat Al Jafri*

PROJECT TITLE: Registry for Children and Adoloscents with Cancer at KFSH&RC for the Children's Omcology Group (COG) Program
RAC# 2141068

PRINCIPAL INVESTIGATOR: *Afshan Ali*

PROJECT TITLE: Clinical Characteristics and Outcome of Pediatric AML In Saudi Arabia: A Multi-Centre Saphos Leukemia Group Study
RAC# 2141150

PRINCIPAL INVESTIGATOR: *Ibrahim Ghemlas*

PROJECT TITLE: HLH Diagnosis, Clinical Features and Treatment Outcome: A Multi-Institutional National Collaborative Retrospective Study by the Saudi Arabian Pediatric Hematology/Oncology Society (Saphos)
RAC# 2151039

PRINCIPAL INVESTIGATOR: *Ali Al Ahmari*

PROJECT TITLE: Hepatoblastoma in Children, A Retrospective Review (2005-2012)
RAC# 2151106

PRINCIPAL INVESTIGATOR: *Basheer Iqbal Ibrahim*
CO-INVESTIGATORS: *Al Fawaz Zakaria Habib, Afshan Ali, Ahmed Al Qatie, Khawar Siddiqui, Mary Grace Barria*

PROJECT TITLE: Prevalence of Hereditarry Cancer Among Children with Cancer in Saudi Arabia
RAC# 2151148

PRINCIPAL INVESTIGATOR: *Abdullah Al-Jefri*
CO-INVESTIGATOR: *Mouhab Ayas*

PROJECT TITLE: A Retrospective Review of Blood & Marrow Transplants in Pediatric Hemoglobinopathies at KFSH&RC, Riyadh, KSA (1993-2014)
RAC# 2151159

PRINCIPAL INVESTIGATOR: *Abdullah Al-Jefri*
CO-INVESTIGATORS: *Amal Al Seraihy, Mahasen Saleh, Mouhab Ayas, Hassan El Solh, Roula Bermada, Ashraf Radwan, Hashan Shahin, Samir Markiz, Ali Al Ahmari, Abdulrehman Al Musa, Ibrahim Ghemlas, Saba Haq, Viqarrudin Khaja, Sohaib Zulfiqar, Ziyad Al Shatnawi*

PROJECT TITLE: HLA Association with Hemophagocytic Lymphohistiocytosis Disease and its Impact on Transplantation Outcome
RAC# 2151207

PRINCIPAL INVESTIGATOR: *Moheeb Ali Alawwami*
CO-INVESTIGATOR: *Ali Al Ahmari*

PROJECT TITLE: NK Cells Impact on Hematopoietic Cell Transplantation Outcome for Severe Combine Immunodeficiency
RAC# 2151102

PRINCIPAL INVESTIGATOR: *Hasan Al Dhekri*
CO-INVESTIGATOR: *Amal Al Seraihy*

PROJECT TITLE: HSCT for Primary Immunodeficiency Disease-Single Center Experience
RAC# 2151103

PRINCIPAL INVESTIGATOR: *Hasan Al Dhekri*
CO-INVESTIGATOR: *Amal Al Seraihy*

PROJECT TITLE: The Outcome of High Risk Neuroblastoma Post Autologous Stem Cell Transplantation: The Experience of King Faisal Specialist Hospital and Research Centre (KFSH&RC)
RAC# 2161023

PRINCIPAL INVESTIGATOR: *Mouhab Ayas*
CO-INVESTIGATOR: *KHULOOD AL-SAYYAD*

PROJECT TITLE: Underlying Genetics of Familial Hemophagocytic Lymphohistiocytosis (FLH) in Saudi Arabia
RAC# 2080041

PRINCIPAL INVESTIGATORS: *Ali Al Ahmari, Abbas Hawwari*
CO-INVESTIGATORS: *Ibrahim Al Fawaz, Mouhab Ayas, Bandar Al Saud*

SELECTED ACHIEVEMENTS

1. Release of Annual Report 2015 from the Central Data Unit.
2. Overall and Event Free Survival Reports on various disease entities of prime significance was estimated using Kaplan-Meier Method and released for the office of the Chairman by the Central Data Unit.
3. Work Requests Automation: Central Data Unit provides administrative and clinical research data pertaining to the Pediatric Hematology/oncology patients to various parties and researchers, besides provision of a variety of services like basic and advanced statistical analysis of data, preparation of research proposals, data collection forms for clinical research, research data repositories, manuscript writing etc. etc. A need was felt to automate the process of Work Requests Approval. An electronic Work Request Form was prepared and Enterprise Correspondence System was used to automate the process of hierarchy of approvals.
4. Hematology Case Ascertainment System: A new system of case accrual for Hematology patients was developed and implemented. This system helps the staff at the Central Data Unit, working in the area of Hematological Disorders to efficiently and effectively accrue patients from the clinics.

5. Computerized Library of Abstracts and Publications: An internet based computerized system of maintaining library of abstracts and publications stemming from the Department of Pediatric Hematology / Oncology was designed and implemented by the Central Data Unit. This system has proved to be extremely helpful in cataloguing the research efforts from the PHO Department and is also available to the office of the Chairman and Deputy-Chairman through the internet.
6. Consultation Capture System: An online Consultation capture system was established by the Hematology Section using the REDCap (Vanderbilt University) data management module enabling primary care providers a universal virtual access to active consultations managed between the two hospitals i.e. KFSHRC & KFNCCC. The system is capable of generating monthly endorsement lists of active consultations resulting in optimization of workforce. The system is responsible for the smooth functioning of the consultation service in relation to improving patient care, better bed utilization, workforce optimization, and well informed comprehensive endorsements of active consultations resulting in better follow-up of patients.
7. Hematology Pre-BMT clearance system: Hematology Pre-BMT Clearance module was created by the hematology section using the REDCap (Vanderbilt University) data management module for an effective Pre-BMT clearance of patients suffering from non-malignant disorders and waiting for a possible BMT. The system was designed to send notifications to the Nurse coordinators for an upcoming due evaluation resulting in a well-structured clinic improving the clearance process. As per the set goals and objectives of the Stem Cell Transplant section an increase in the number of transplants by 3% was expected by the MCA and it was observed that the online Pre-BMT Clearance system helped in the effective clearance of pre-BMT hematology patients in a timely fashion supporting the SCT section in achieving the strategic goal of the department i.e. increase number of transplants.
8. EndNote – Computerized Reference Manager. Literature search and placement of references is one of the most tiresome and tedious component in writing of a research manuscript if one works without a reference manager. We acquired state of the art reference manager called EndNote from Thomson Reuters, both Desktop and Web version at the Central Data Unit. This software is capable of managing references from various sources and inserting them into the manuscript automatically. The application was setup for Consultants, Assistant Consultants, Fellows and researchers and one-on-one training sessions were provided for those who needed help. The web-enabled version of the software was obtained without incurring any cost to the KFSH&RC.
9. A special computer programming language "R" was acquired to perform highly sophisticated statistical analyses for our HSCT patient population, at the Central Data Unit. This language is being used to do the above mentioned analyses for various projects, abstracts and publications. An upgraded version of this language capable of performing additional tasks was obtained and installed for operations. This was done without incurring any cost to the KFSH&RC.
10. PIMS Bone Marrow Transplant Module was Upgraded for addition of new data items for the Central Data Unit.
11. The Central Data Unit is playing a critical role in implementation of a newly initiated program from the Office of the Chairman, PHO

Department to write manuscripts from the abstracts that were prepared and presented into various national and international conferences but were never written down as publications. In this regard, the CDU is involved with four teams of researchers who have started working on writing papers on Gliomas, Medulloblastoma, rare-bleeding disorders and Atypical-Teratooid Rhabdoid Tumors (ATRT). We are providing training on writing manuscripts, use of reference manager software like EndNote and statistical analysis of the data.

12. Specially designed training course of one month duration "Basics of Clinical Research and Data Management" program to provide training to the newly commissioned Fellows at the Department was initiated. The objectives of the program were to provide in depth knowledge in designing and conducting clinical research, collection, collation and management of data using computerized databases and hands-on training on SPSS for Windows version 20 for statistical analyses of the clinical and research data. This program was initiated on a special request from the Director of the Fellowship Program at the PHO Department by the Central Data Unit.

PUBLICATIONS

YEAR 2015

- Al-Kofide, A., Central Nervous System Germinoma. Article for Medscape 2015. (http://emedicine.medscape.com/article/281714-overview).
- Al-Saud, B. Al-Mousa, H. Al-Ahmari, A. Al-Ghonaium, A. Ayas, M. Alhissi, S. Al-Muhsen, S. Al-Seraihy, A. Arnaout, R. Al-Dhekri, H. Hawwari, A., Hematopoietic stem cell transplant for hyper-IgM syndrome due to CD40L defects: A single-center experience. *Pediatr Transplant* 2015.
- Al Ahmari, A., Is secondary hemophagocytic lymphohistiocytosis behind the high fatality rate in Middle East respiratory syndrome corona virus? *Journal of Applied Hematology* 2015.
- Mehta, P. A. Zhang, M. J. Eapen, M. He, W. Seber, A. Gibson, B. Camitta, B. M. Kitko, C. L. Dvorak, C. C. Nemecek, E. R. Frangoul, H. A. Abdel-Azim, H. Kasow, K. A. Lehmann, L. Vicent, M. G. Diaz Pérez, M. A. Ayas, M. Qayed, M. Carpenter, P. A. Jodele, S. Lund, T. C. Leung, W. H. Davies, S. M., Transplantation Outcomes for Children with Hypodiploid Acute Lymphoblastic Leukemia. *Biol Blood Marrow Transplant* 2015.
- Mouhab Ayas. Unrelated Hematopoietic Cell Transplantation in Aplastic Anemia. There Is More To a Successful Outcome Than Meets the Eye. *JAMA Oncol* 2015.
- Orchard, P. Fasth, A. Le Rademacher, J. He, W. Boelens, J. Horwitz, E. Al-Seraihy, A. Ayas, M. Bonfim, C. Boulad, F. Lund, T. Buchbinder, D. Kapoor, N. O'Brien, T. Diaz Perez, M. Veys, P. Eapen, M., Hematopoietic stem cell transplantation for infantile osteopetrosis. *Blood* 2015.
- Dufour, C. Pillon, M. Sociè, G. Rovò, A. Carraro, E. Bacigalupo, A. Oneto, R. Passweg, J. Risitano, A. Tichelli, A. Peffault de Latour, R. Schrezenmeier, H. Hocshmann, B. Peters, C. Kulasekararaj, A. Van Biezen, A. Samarasinghe, S. Hussein, A. A. Ayas, M. Aljurf, M. Marsh, J., Outcome of aplastic anaemia in children. A study by the severe aplastic anaemia and paediatric disease working parties of the European group blood and bone marrow transplant. *Br J Haematol* 2015, 169 (4), 565-73.
- Ayas, M. Eapen, M. Le-Rademacher, J. Carreras, J. Abdel-Azim, H. Alter, B. P. Anderlini, P. Battiwalla, M. Bierings, M. Buchbinder, D. K.

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DEPARTMENT OF PEDIATRICS

DEPARTMENT OF PEDIATRICS

CHAIRMAN

Prof. Ibrahim Bin-Hussain, MD

PEDIATRIC RESEARCH COMMITTEE CHAIRMAN

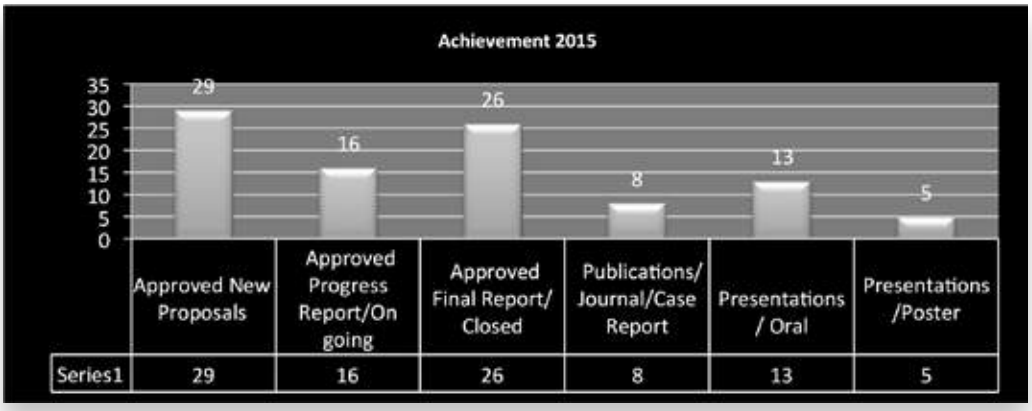
Wajeeh Al-Dekhail, MD

THE DEPARTMENT OF PEDIATRICS NEVER STOPS SEEKING FOR improving the quality of its services in all aspects as patient care, teaching and research. The Department of Pediatrics is one of the largest medical departments at KFSH&RC. It consists of ten subspecialty sections: Allergy/ Immunology, Endocrinology/ Diabetes, Gastroenterology, General Pediatrics, Infectious Diseases, Neonatology/ Perinatology, Nephrology, Pediatric Intensive Care, Pulmonology and Rheumatology. They provide children medical treatment of a highly specialized nature, promoting medical research and education programs including post-graduate including accredited fellowship training programs and contribute to the prevention of diseases.

Residents and Fellows are heavily involved in conducting Research Projects with high level of achievements in 2015. This report summarizes RAC approved projects that were initiated, on-going and completed for 2015. During the year 2015, the Department of Pediatrics has continued to perform its variety of activities to provide the best patient care, which constitute Research projects, and many educational activities through workshops, International forums, and Pediatric Training Sessions.

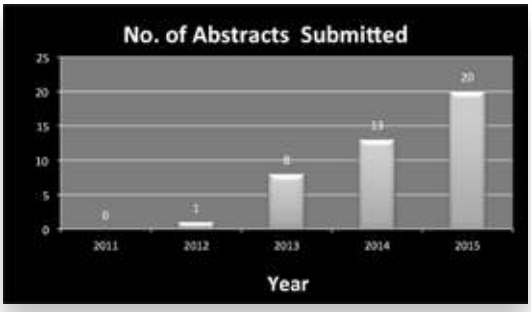
In order to promote research, the department conducted Pediatric Research Day on 11 January 2015 with over 37 Abstract submitted.

At the end of 2015, the Department of Pediatrics has 26 Publications, 13 abstracts presented individually and in collaboration with other departments at KFSHRC&RC and internationally. We have 45 RAC approved ongoing projects include Retrospective and prospective studies.

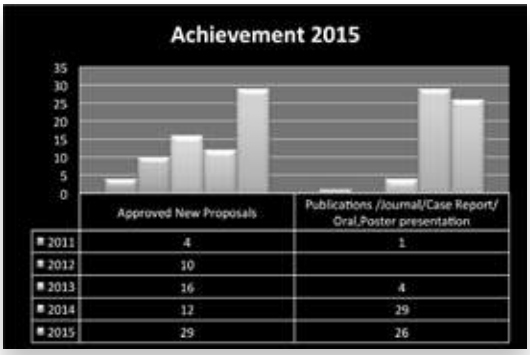


SELECTED ACHIEVEMENTS

1. The involvement of the Department in the Annual KFSH&RC Residents' Research Day has increased dramatically over the past years.



2. Increased number of Approved New Research Proposal and Publications.



3. Collaborative studies with National and International Institutions.

INTERNATIONAL

- DUKE UNIVERSITY MEDICAL CENTER (DUMC).
- Cincinnati Children Hospital Medical Center (CCHMC), Burnet Ave, USA
- Inborn Errors working party (IEWP) /European Society for Blood and Morrow Transplantation (EBMT) /European Society for Immunodeficiency (ESID). Geneva, Switzerland.
- Sultan Qaboos University Hospital (SQUH), The Royal Hospital (TRH).

NATIONAL

- King Saud University, Riyadh, KSA.
- AL Habib Hospital, Riyadh, KSA.
- King Abdul-Aziz City for Science and Technology (KACST), KSA.
- Department of Pathology & Laboratory Medicine, KFSHRC, Riyadh, KSA.
- Department of Medicine, KFSHRC, Riyadh, KSA.
- Department of Medical Genetics, KFSHRC, Riyadh, KSA.
- Department of Oncology, KFSHRC, Riyadh, KSA.
- Organ Transplant Center, KFSHRC, Riyadh, KSA.
- Biostatistics, Epidemiology And Science Computer, KFSHRC, Riyadh, KSA.

- Quality Management, KFSHRC, Riyadh, KSA.
- Al FAISAL University, Riyadh, KSA.

4. Training Students / Employees in different aspects, methods, tasks, procedures of the registry.
5. In order to promote research, the department conducted Pediatric Research Day on 11 January 2015 with over 37 Abstract submitted.

RESEARCH PROJECTS

PROJECT TITLE: PFN R01 – Pediatric Candidiasis Biomarkers
RAC # 2151124

INVESTIGATORS: *Ibrahim Bin Hussain, Abdullah Al-Turki, Sahar Thwadi, Ohoud AlYabes, Sami AlHajjar, Suliman AlJumaah, Haysam Tufenkeji, Jihan Hassenein, Manal AlShaikh*

ABSTRACT: Invasive candidiasis is associated with significant morbidity and mortality in immunocompromised children. This project will address whether biomarkers can improve the time to diagnosis of Candida infections as compared to traditional blood cultures. Additionally, these same biomarkers will be evaluated to measure response to treatment.

Invasive candidiasis is a common and frequently fatal infection in high-risk hospitalized children. The current standard of care to diagnose Candida infections is blood cultures. However, due to the long lag time between obtaining blood and receiving culture results, appropriate antifungal therapy is often delayed. Utilization of fungal biomarkers could decrease the time to diagnosis of Candida infection, allowing appropriate therapy to be started earlier.

In order to accomplish the aims, this study will assemble a prospective cohort of pediatric patients at high-risk for developing invasive candidiasis. Blood samples for biomarker testing will be obtained at the time a patient has a clinical indication for blood culture attainment. To accomplish the second aim, additional blood sampling will be performed in the sub-set of patients that are found to have invasive candidiasis. For the third aim, leftover blood samples following biomarker testing from all consenting participants will be stored in a biobank. This biobank will be used to examine future, currently undeveloped, biomarker assays in an effort to further reduce the time to diagnosis of invasive candidiasis.

This is a multicenter study currently composed of 39 sites as part of the already established International Pediatric Fungal Network (PFN; www.ipfn.org). We anticipate approaching additional sites to join this Network during the study period. Each site will be required to obtain local IRB approval before enrolling patients in this study. Additional blood samples at defined timepoints will be performed in this subset of patients to determine the change in biomarker expression in response to antifungal therapy. For Aim 3, we will retain leftover serum samples from study participants to create a biobank for future biomarker studies.

AIMS

- Define the operating characteristics of fungal biomarker assays in pediatric patients at high-risk for developing invasive candidiasis
- Determine the change in fungal biomarker assay results in those children who developed invasive candidiasis in order to monitor their response to therapy
- Create a biobank of blood samples from pediatric patients at high risk for invasive candidiasis and those with invasive candidiasis for future testing

of fungal biomarker assays and development of new fungal biomarker assays.

PROJECT TITLE: Correlation and Responsiveness of Cutaneous Lupus Disease Area and Severity Index (CLASI) and Skindex-29 with Cutaneous Childhood Lupus Erythematosus
RAC # 2151198

INVESTIGATORS: *Sulaiman Al-Mayouf, Ashwaq AlEed, Hermine Brunner, Norah AlMutairi*

ABSTRACT: Up to 85% of patients with systemic lupus erythematosus (SLE) have SLE-specific and/or nonspecific cutaneous lesions, often intricately combined, during both acute and chronic phases. However, the cutaneous manifestations of SLE are among the least systematically studied aspects of this autoimmune illness.

This has resulted in part from the lack of validated tools to determine the impact of therapy on the activity of the cutaneous manifestations of SLE. Because the skin is the second most commonly involved organ in patients with SLE a clinical measure to quantify the activity and chronicity of cutaneous involvement, the Cutaneous Lupus Disease Area and Severity Index (CLASI), has been developed. This instrument was developed and has been used in adults. However, its usefulness in children and adolescents with SLE has not been studied.

SLE disease activity and damage have been reported to predict both a reduced health-related quality of life (HRQOL) and to increase economic burden. The Skindex-29 has been developed and validated as an instrument to measure the HRQOL in patients with skin disease.

AIMS

- To assess the correlation between the CLASI and HRQOL as measured by the Skindex-29 in children and adolescent with cutaneous SLE.
- To observe the difference in these correlations between affected patients (children and adolescents with cutaneous SLE) and controls (patients with juvenile idiopathic arthritis, JIA)
- To compare the correlations observed in two different centers with similar SLE populations

PROJECT TITLE: Genetics of Familial Rheumatic Diseases
RAC # 2150024

INVESTIGATORS: *Sulaiman M Al-Mayouf, Salma Majid, Dorota Monies, Abdullah Alsonbul, Brain Meyer*

ABSTRACT: Rheumatic diseases are heterogeneous conditions characterized by articular manifestations. However, certain diseases such as systemic vasculitis and systemic lupus erythematosus (SLE) might present with serious multi-organ involvement in addition to articular manifestations. Although rheumatic diseases rarely occur as familial diseases, many detailed family studies of rheumatic diseases with first-degree relatives, examining genetic predisposition have been published, relatives of children with autoimmune diseases have been shown to have an increased prevalence of the same diseases and probably other forms of autoimmunity.

Juvenile idiopathic arthritis (JIA) is the most common form of childhood arthritis. At King Faisal Specialist Hospital and Research Center (KFSH-RC), we are seeing patients with heterogeneous inflammatory including JIA, SLE and auto inflammatory disorders and non-inflammatory disorders. Interestingly, it is not uncommon to see patients with first-degree relatives having the same disease. Recently, we reported 13 patients with systemic onset JIA (So-

JIA) from 5 consanguineous families. Our findings showed a strong genetic evidence of a monogenic autosomal recessive form of So-JIA associated with mutation of LACC1.

In this study, we propose to apply the latest molecular techniques to search for the underlying genetic defect in these families. Identified gene(s) will then be tested in a larger cohort of sporadic corresponding cases to further clarify the role they play in the more common form of this disease.

AIMS

- To perform genome wide linkage analysis in multiplex Saudi families with rheumatic diseases and inherited arthropathy.
- To test the contribution of the identified risk loci of the familial cases among sporadic cases.

PROJECT TITLE: Juvenile Idiopathic Arthritis in Multiplex Families: Longitudinal Follow-up
RAC # 2141114

INVESTIGATORS: *Sulaiman Al-Mayouf, Munira AlMari, Alya Qari, Abdullah Alsonbul*

ABSTRACT: Juvenile idiopathic arthritis (JIA) is a phenotypically heterogeneous group. Etiology and pathogenesis of JIA are not well defined yet. However, both genetic and environmental factors are thought to influence disease susceptibility and expression. Family history of JIA is not considered in the current classification criteria of JIA. Despite familial aggregation of JIA is rare, the recurrence rate is highest among the first-degree relatives. Couple of cohorts of siblings with JIA from Europe and United states showed early disease onset and diagnosis and high concordance for gender, onset type and course type.

The previous reports did not describe the long-term longitudinal follow of siblings with JIA.

Here, at our institution, we followed a large cohort of familial JIA from consanguineous families for several years. The pedigrees of the multiplex JIA families clearly indicate an autosomal recessive pattern of inheritance. In this study, we will describe the extended family pedigrees of JIA multiplex families and the clinical phenotype with longitudinal physical and social status follow-up.

AIMS: To describe the extended family pedigrees of JIA multiplex families and the clinical phenotype with longitudinal physical and social status follow-up.

PROGRESS: Ongoing.

PROJECT TITLE: Childhood Pancreatitis at a Tertiary Care Center in Saudi Arabia
RAC # 2121163

INVESTIGATORS: *Ali Al-Mehaidib, Husam Islam, Wajeeh Al-Dekhail, Saleh AlNassar*

ABSTRACT: Pancreatitis is an inflammatory disease of the pancreases. Clinical features are abdominal pain and elevated levels of pancreatic enzymes in the blood. Although it is not common, pancreatitis is associated with significant morbidity and mortality. Diagnosis is based on clinical signs of abdominal pain, accompanied by a threefold increase in either amylase or lipase.

The aim of this study is to define the most common cause of pancreatitis in children seen at a tertiary care center in Saudi Arabia, review the clinical presentation, management, and outcome of pediatric patients with Pancreatitis in Saudi Arabia.

This is a retrospective study for the diagnosed patients with pancreatitis between 2002-2012 in King Faisal Specialist Hospital and Research Centre (KFSH&RC).

It is important to identify the causes of pancreatitis in order to limit diagnostic approach and decrease cost. Our study will show the significance of the clinical presentation and early intervention in the management of the disease.

AIMS: The aim of this study is to review the clinical presentation, diagnosis, etiologies, management, and outcome of pediatric patients with pancreatitis in Saudi Arabia.

PROGRESS: Ongoing.

PROJECT TITLE: A Retrospective Clinical and Molecular Genetic Characterization of 25-Hydroxylase Deficiency in Saudi Patients.
RAC # 2151206

INVESTIGATORS: *Afaf AlSagheir, Faiqa Imtiaz, Sarah Bakhamis, Osamah AlSagheir, Abdulrahman AlRajhi*

ABSTRACT: Vitamin D deficiency is becoming a worldwide issue, and it's a major cause of rickets in infants, children and adolescents. The synthesis of bioactive vitamin D requires hydroxylation at the 25 and 1-α positions by cytochrome P450 enzymes in the liver and kidney, respectively. Many genetic and biochemical evidence showed that CYP27B1 is the one encoding 1α-hydroxylase enzyme that forms the bioactive form of 1, 25-dihydroxyvitamin D. Several cytochromes P450 (CYP) can catalyze the 25-hydroxylation step in the liver, including CYP2C11, CYP2D25, CYP3A4, CYP2J1, CYP27A1, and CYP2R1.

Nowadays, many studies are proofing CYP2R1 to be the primary key for the 25-hydroxylation in the liver. In the current study, we describe (No. of pts or families) who proved to have mutations in CYP2R1 (25-hydroxylase deficiency). We intend through chart reviews, to gather the clinical, endocrinological, and molecular data related to these patients and we believe this study to be the largest cohort study.

AIMS: To retrospectively describe the full clinical and genetic basis of 25-hydoxylase deficiency in Saudi Arabian patients.

PROJECT TITLE: Bile Acid Synthesis Disorders: A Case Series
RAC # 2141136

INVESTIGATORS: *Wajeeh Al-Dekhail, Haifa Alawadhi, Ali Al-Mehaidib, Khalid Al-Saleem, Mohammed Banemai*

ABSTRACT: Bile acids (BA) are essential for the normal hepatic function and metabolism. Children who lack BA synthesis may end up with liver cirrhosis leading to transplantation. Such children usually present in early childhood with signs and symptoms of cholesteric jaundice that might not be distinguished from other causes. Patients may present even in adulthood, making it an important differential diagnosis.

Clinical presentation is usually that of cholesteric jaundice, but with a normal GTT level and atypical BA in urine and serum identified by mass spectrometry.

Important to highlight is that treatment of BA synthesis is entirely accessible with oral administration of BA replacement therapy. In addition, prevention of irreversible cirrhosis is

possible with early administration of treatment, before histological changes.

However, this group of disorders remains a rare group that has not been well described yet. Enough understanding of the basis of it is still lacking, making it more difficult to identify those at risk.

An important factor is consanguinity that is highly prevalent in the Saudi community. This makes it even more desirable to identify the patterns of the disease in this society, aiming to find pattern that are unique to this population.

AIMS: This case series is expected to provide the following:

- A description of the clinical presentation and outcome of Saudi Patients diagnosed to have bile acid synthesis disorders along with their specific gene disorders.
- It will give an update on the most common mutations and trends in Saudi patients presenting to KFSH&RC.
- A large multicenter descriptive study that will add to the pool of information of this rare treatable disorder is planned along with a future establishment of a national registry for BASD.

PROGRESS: Ongoing.

PROJECT TITLE: Bone Health Care in Children with Chronic Conditions: A Retrospective Study
RAC # 2151174

INVESTIGATORS: *Fawzah AlRwaili, Walaa AlShammasi, Afaf AlSagheir*

ABSTRACT: Vitamin D and calcium are important elements in prevention of osteopenia and pathological fractures in pediatrics and adult. Recent studies indicate very important other benefits of normal vitamin D level e.g. enhancing immunity and protection from autoimmune disease by modulating the function of activated T and B lymphocyte. Vitamin D and calcium status can be assessed by measuring their blood level and confirmed by doing bone x-ray and/or DEMSA scan.

Low BMD is prevalent in children with moderate and severe CP and is associated with significant fracture risk.

Children with chronic multiple medical condition who had 2 or more organ involved are at great risk of the development of osteopenia and fractures than others. We conducted a retrospective study in King Feisal Specialist Hospital and Research center, we included 200 patients who is age between 1-14y/o, who have 2 or more health problems, both hospitalized and out patients. Charts were reviewed for Demographic, Gastrointestinal complications Seizure (+/- antiepileptic medications).

Feeding history (way of feeding, type of formula, amount of formula, calculated calcium and vitamin D amount within the formula) if obtainable,

The anticipated result of increasing prevalence of osteopenia in children with multiple medical issues. Also will find out less children with chronic multiple medical issues who are at risk of osteopenia on vitamin D supplements or at least investigated to role out osteopenia

Children with multiple chronic medical issues at increasing risk of osteopenia and need to be screened for that.

AIMS: To assess bone health care in chronic pediatric patients followed up or admitted to King Faisal specialist hospital and research center.

PROJECT TITLE: Child Safety and Injury Prevention

INVESTIGATORS: *Fouzah Alrowaily, Hoda Kattan, Eyad AlMidani, Manal AlShaikh, Kris Hervera, Huda Alharbi, Weam Elsaidawi*

ABSTRACT: Health care providers and hospitals have played a key role in providing awareness, education, and access to equipment to improve children safety, and in order to understand the essence of the problem and to find out the most common misconceptions, we will implement a survey questionnaire to test the knowledge, attitudes and behavior of health care workers regarding child injury prevention before and after education programs,

This project is to educate the awareness of healthcare providers about child safety and injury prevention. A survey will be conducted among healthcare providers, who works in the out-patients and in-patients, through an anonymous, self-administered questionnaire (attached), to assess their knowledge, and then we will start the child safety and injury prevention education programs in form of personal interaction with printed educational materials and a media campaign for 3 months in King Faisal specialist hospital in Riyadh, then the same questionnaire will be distributed to similar group of population, to see the impact of the education programs in increasing the knowledge. 160 people were involved in this study (75 % were female and 25% were males), pediatricians answered accurately most of the questions considering knowledge than the other groups. More than 70% of respondents identified correct answers to 16 questions about attitudes towards child injury prevention and safety promotion. This study, which shows the current level of knowledge, attitudes and behavior patterns of parents and health professionals in KFSH&RC (Riyadh, KSA), could help in the preparation of appropriate prevention programmers.

AIMS: The aim of this project is to educate and increase the awareness of healthcare providers about child safety and injury prevention, and to make a clear policy at a local level to be implemented in other hospitals in the Kingdom

PROGRESS: Ongoing.

PROJECT TITLE: Clinical Significance of IgM Deposition in the Poor Outcome of Pediatric Minimal Change Disease: Single-center Case-Control Study
RAC # 2141144

INVESTIGATORS: *Turki Al-Shareef, Duaa Al Romaili, Turki Al Hussain*

ABSTRACT: The course of pediatric minimal change disease (MCD) usually has good prognosis. However, in less common presentation, MCD can have a poor course making renal biopsy-Immunofluorescence (IF) a must to identify the cause. Immunoglobulin M (IgM) occasionally deposits in kidney mesangium and is seen under electron microscopy. The rule of IgM is controversial. It is believed it is associated with unusual poor prognosis as per kidney function deterioration, poor response to steroid.

We reviewed 212cases of children with MCD who underwent renal biopsy at KFSH-Riyadh from 2003 to 2014.The sample was divided according to IgM deposition under IF: Case group with IgM present under IF (IgM+IF n=85), and control group with no IgM under IF (IgM-IF n=127). We reviewed hypertension, hematuria and IgM serum level at time of presentation, the response to

corticosteroid therapy (dependence, resistance and frequent relapses)the response after start of immunosuppressive therapy(complete remission, partial remission, and no response) and development of chronic kidney disease(CKD).

IgM+IF showed significant association with hypertension at time of diagnosis (p=0.041). Increase in median relapses per year was significantly associated with IgM+ IF.In terms of response to corticosteroid, there was statistical significance association of IgM deposition with development of steroid-dependence(p=0.038). CKD developed in 18% of IgM+ IF with p= 0.041.

MCD with IgM+ IF can be a marker of the disease severity in pediatrics. IgM Deposition reveals poor response to corticosteroid. A prospective study is required to verify this conclusion

AIMS: The aim of this study is to examine the clinical significance of IgM serum level and mesangial IgM deposition in IF in predicting the outcome of nephrotic syndrome in children with IgM+ IF nephrotic syndrome.

PROGRESS: Ongoing.

PROJECT TITLE: Vitamin D and Its Correlation with Bone Mineral Density and Disease Activity in Childhood Systemic Lupus Erythematosus

INVESTIGATORS: *Sulaiman M Al-Mayouf, ALHanouf ALSaleem*

ABSTRACT: Children with SLE enrolled in a cross-sectional study evaluated for disease activity, which is completed by using the SLE Disease Activity Index (SLEDAI), vitamin D profile, bone markers and BMD of the lumbar spine (LS) and the whole body (WB) using Dual Energy X-ray Absorptiometry at enrollment and 6 months later. All patients treated with cholecalciferol (vitamin D3) 2000 IU daily and calcium supplement (caltrate 600) mg twice daily.

Twenty-eight patients (26 female) completed the evaluation. Mean age 9.7 + 3.2 years with mean disease duration of 5.4 + 4.3 years. Mean baseline 25-OH vitamin D level was 54.1+ 30 nmol/L, and SLEDAI score was 5.7 + 4.7. BMD was subnormal in 23 patients, with mean baseline (Z-score) of LS and WB (-1.6+ 1.1, – 0.5+ 1 respectively). Levels of vitamin D correlated inversely with SLEDAI and positively with bone density but did not reach statistical significance. Bone markers levels correlated with BMD. After 6 months treatment with cholecalciferol and caltrate, BMD of LS and WB didn't show significant improvement (-1.6+ 1.2 and WB – 0.6+ 1 respectively). However, there was significant improvement in disease activity correlating with the improvement of 25-OH vitamin D levels.

Our findings indicate that low BMD is common in childhood SLE. Furthermore, daily vitamin D supplementation could improve the serum levels of 25-OH vitamin D and disease activity. However, there was no improvement in BMD during treatment period with the proposed 25-OH vitamin dose.

AIMS: To determine the effect of vitamin D supplement on bone mineral density (BMD) in children with systemic lupus erythematosus (SLE) and its correlation with disease activity.

PROJECT TITLE: Juvenile Dermatomyositis in Arab Children: Clinical Features and Long-term Outcome
RAC # 2141098

INVESTIGATORS: *: Sulaiman M. Al-Mayouf, Nora AlMutairi, Abdullah Sonbul*

ABSTRACT: Juvenile dermatomyositis (JDM) is a multisystem inflammatory disease affects primarily the skin and muscles. Typically, patient presented with proximal muscle weakness and characteristic skin rash with elevated muscle enzymes.

The goal of treatment is to control inflammation and normalize muscle strength as well as to improve quality of live and function and to minimize the potential complication namely, calcinosis. The available published data from Arab countries about JDM is very limited. Only, one Saudi cohort from our center retrospectively described the clinical manifestations and disease course of 25 children with JDM but no data from other Arab countries to compare the disease expression and outcome. Furthermore, data on long-term clinical outcome of JDM and its impact are not published yet.

This work is a multicenter review; we will highlight the clinical manifestations and long-term outcome of JDM and its impact on education and quality of life.

AIMS

- To report the clinical manifestations of JDM children from 3 Arab countries (Saudi Arabia, Jordan, and Oman).
- To highlight the quality of life and long-term outcomes
- To compare the results with other cohorts from different ethnicities.

PROGRESS: Ongoing.

PROJECT TITLE: Crème in the Lungs; Silent Killer

INVESTIGATORS: *Sami AlHaider, ALHanouf ALSaleem*

ABSTRACT: Lipoid pneumonia is a rare disorder, caused by lipid accumulation in the alveoli, leading to significant lung damage. Exogenous lipoid pneumonia in children represents a preventable serious complication of improper use of high-lipid containing nutritional supplements.

This is a case study of a pediatric patient seen by pulmonology team in KFSH&RC, Riyadh, KSA, under the age of 14years. Patient's family interviewed with Ethical consideration. Medical record was analyzed with confidentiality.

We are reporting a challenging 3 month old infant with history of persistent and progressive respiratory distress not responding to medical treatment. History revealed prolonged (4 weeks) butterfat ingestion as nutritional supplement since the age of 2 weeks. The information of lipid ingestion was repeatedly denied by parents in the earlier course of presentation.

Our patient course was complicated with superimposed mycobacterium Fortituim infection and lung abscess formation that required anti-mycobacterial combination therapy, systemic corticosteroids, a trial of therapeutic Broncho alveolar lavage, and surgical excision with debridement. Improving the awareness of exogenous lipoid pneumonia in the community can lead to elimination of harmful cultural habits and can ultimately reduce mortalities and morbidities related to this condition.

We have concluded that physicians shall always have clinical sense in suspected cases and to anticipate hidden history of relevant information's. Furthermore our societies need to be educated about common cultural behavior, which may harm our children unintentionally, leading to preventable fatal complications.

PROJECT TITLE: Hematopoietic Stem Cell Transplantation Survival in SCID Children from Saudi Arabia: A Retrospective Analysis of Transplants (1993-2015)
RAC # 2051052

INVESTIGATORS: *Saleh AlMohsen, AlHanouf AlSaleem*

ABSTRACT: This is a retrospective cohort comprising all pediatric patients below the age of 14 years admitted at KFSH&RC, Riyadh with the final diagnosis of SCID whom Underwent SCT between December 1993 and September 2015.

Total of 253 SCT were performed on 234 SCID patients. Median age of diagnosis 3.7 months. More than half of the patients received BCG vaccine. Pretransplant showed that 27.5% had positive CMV infection, and rest had diverse clinical manifestations. Myeloablative conditioning was given to one third of patients 32.4%, and reduced-intensity treatment (18.6%). Overall survival rate was 73.1%. Patients with (T^- B^-) and (T^- B+) had the best outcome (75.2%, 77.4% respectively). Patients whom were transplanted with an age of <3months had the highest survival (80.4%). Matched related donors had a higher survival rate (Phenoidentical 85%, genoidentical 79.3%), Haploidentical (66.7%), lowest survival observed with mismatched HLA. In relation to conditioning there was no significant differences in survival (75.8% no conditioning, 72.6% Myeloablative regimen). Immune constitution were significantly higher compared to pretransplantation with a P-value <0.0001. Secondary complications were mostly acute GVHD in 30.4% followed by bacterial/viral Infections. Death was encountered in 26.9% with a Sepsis as a main cause. 164 patient had successful engraftment 117 of them are cured and off treatment.

We have concluded that the earlier the diagnosis and transplant intervention the better the prognosis. Pretransplant Risk factors had significant impact on the outcome.

AIMS: To assess the overall rate of survival in children with SCID who received SCT and determine the clinical manifestations pre and post-transplant and its affect upon the prognosis.

PROJECT TITLE: Allogeneic Stem Cell Transplantation for Hyper-IgM Syndrome: A Single Center Experience
RAC # 2131110

INVESTIGATORS: *Bandar Al-Saud, Abdulaziz Al-Ghonaium, Hamoud Al-Mousa, Hasan Al-Dhekri, Saleh Al-Muhsen, Rand Arnaout, Amal Al-Seraihy, Abdullah Al-Jefri, Mouhab Ayas, Ali Al-Ahmari, Hassan El-Solh*

BACKGROUND: Hyper IgM syndrome due to CD40 and CD40L deficiency is a rare form of combined immunodeficiency disease. Stem Cell Transplantation (SCT) has been considered the only cure for this disease. Data from a single center experience around the world and especially from our area are limited so far.

AIMS: To determine the outcome of SCT in patients with hyper-IgM syndrome at King Faisal Specialist Hospital and Research Centre (KFSH&RC) and to evaluate the toxicity profile of the transplantation procedure in this cohort of patients.

PROGRESS: Ongoing.

PROJECT TITLE: Conginetal Lipoid Adrenal Hyperplasia Due to Star Mutations.
RAC # 2151 206

INVESTIGATORS: *Afaf AlSagheir, Doha AlHumaidah, Bassam Bin Abbas, Ebtesam Qassem, Meshael Alswailem*

ABSTRACT: Congenital Lipoid Adrenal Hyperplasia is an extremely rare cause of CAH. Most cases are due to mutations in the steroidogenic acute regulatory protein (StAR), a mitochondrial phosphoprotein that mediates transport of cholesterol from the outer to the inner mitochondrial membranes. More than 35 inactivating mutations have been described in StAR. We describe 3 cases of CAH.

We describe the clinical and genetic bases of 3 patients with CAH secondary to StAR mutations. Molecular testing was performed on genomic DNA isolated from peripheral leucocytes using PCR and direct Sanger sequencing of all exons and exon-intron boundaries of StAR gene. This was compared with normal sequence using Ensemble and NCBI databases.

RESULTS

Patient 1: A 13-year old girl born to consanguineous parents. She presented at 1 month of age with increasing pigmentation and hypotensive crisis. She had normal female external genitalia. She was treated with hydrocortisone and fludrocortisone and did well.

Patient 2: A 22-year old girl born to consanguineous parents. At 2 weeks of age, she presented with dark skin and hypotensive crisis. She had normal female external genitalia and palpable undescended testis.

Patient 3: A 7 year old with 46XY karyotype. She developed hypotensive crisis and skin pigmentation at 3 weeks of age. She had normal female external genitalia.

StAR mutations lead to severe form of CAH. This report describes the clinical, biochemical and genetic bases of 3 cases with this extremely rare syndrome including a novel mutation.

PROJECT TITLE: Liver Disease in Cystic Fibrosis Patients
RAC # 2151155

INVESTIGATORS: *Wajeeh Al-Dekhail, Hanaa Banjar, Najlaa Abdulaziz, Sami Alhaider,Imran Nizami, Ibrahim AlMogarri*

ABSTRACT: Cystic fibrosis-associated liver disease (CFLD), is now considered the third cause of death, after lung disease and transplantation complications. It is estimated to affect up to 30% of CF patients. Clinical symptoms appear late in the course of the disease, when hepatobiliary system damage is already very advanced.

After obtaining the ethical approval, retrospective files reviewed for patients of CF from KFSH&RC CF registry. Multiple variable were collected and analyzed including: ALT, AST, GGT, Alkaline phosphatase, bilirubin, Albumin, INR and US liver findings.

363 CF patients were involved in the study, 194 females and 169 males. 3 % of them had high liver enzyme and started on Ursodeoxycholic Acid. Some of the patient developed chronic liver disease changes including fatty infiltration, steatosis and cirrhosis in Ultrasound test.

In comparing our result with the previous study which was done 1994 at KFSH&RC, there is improvement in liver outcome in CF patients due to early detection and treatment. Early detection and treatment of cholestasis will prevent the development of liver cirrhosis.

AIMS: To determine the incidence of liver disease in our CF population and to determine the factors that increases the risk for developing cirrhotic liver disease.

PROJECT TITLE: Mutational Analysis of CYP11B1 in Patients with 11-ß Hydroxylase Deficiency
RAC # 2151 206

INVESTIGATORS: *Afaf AlSagheir, Doha AlHumaidah, Bassam Bin Abbas, Ebtesam Qassem, Meshael Alswailem*

ABSTRACT: 11-ß hydroxylase deficiency is the second most common cause of congenital adrenal hyperplasia (CAH). Mutations in CYP11B1 are the underlying genetic abnormality in patients (pts) with this condition. Mutational analysis of 11 patients from 6 unrelated families revealed several novel mutations.

In 46XX subjects (8 pts), the clinical presentation varied between clitromegaly only to complete ambiguous genitalia (AG) and normal uteri and ovaries. In all cases, the biochemical profile showed variable but consistent pattern with low basal and stimulated cortisol, extremely elevated 11 deoxycortisol (2 to 60-fold), and significantly elevated ACTH.

RESULTS

Family 1: Three siblings with 46XX presented at ages between 2 to 16 years with AG. Their 46XY sibling had accelerated growth and precocious puberty. leading to frameshift and truncation at codon 39.

Family 2: Two 46XX siblings with clitromegaly only. Mutational analysis revealed a novel mutation (c.1343G>C, p.488R>P). Both chose female gender.

Family 3: One 46XY and one 46XX siblings. Mutational analysis showed a previously described mutation (c.1394A>T, p.465H>L

Family 4: 46XX with AG. Genetic analysis revealed a novel nonsense mutation (c.780G>A, p.260W>X).

Family 5: a 1-year old 46XX presented with ambiguous genitalia. Molecular analysis showed a missense mutation (c.617G>T, p.206G>V).

Family 6: A 46XY presented with accelerated growth and precocious puberty. Mutational analysis showed a missense mutation (c.1343G>C, p.448R>P).

We described 11 pts of 11 ß hydroxylase deficiency with variable clinical and biochemical profiles and a number of novel mutations ofCYP11B1. The cases illustrate the phenotypic, genetic and gender identity heterogeneity.

PROJECT TITLE: Phenotypic and Genotypic Features of 10 Saudi Patients with 5 alpha Reductase Type 2 Deficiency
RAC # 2130018

INVESTIGATORS: *Afaf AlSagheir, Ohoud AlZahrani, Ali AlZahrani, Bassam Bin Abbas, Ebtesam Qassem, Meshael Alswailem*

ABSTRACT: Five alpha reductase type 2 deficiency is a rare form of 46 XY DSD, resulting in impairment of testosterone (T) conversion to its more active metabolite dihydrotestosterone (DHT), which is crucial for the differentiation of the male external genitalia and prostate. The clinical picture of 5 alpha reductase deficiency types 2 is variable, ranging from female to a fully male phenotype with hypospadias or only micropenis. In this article, we report the clinical and molecular data of SRD5A2

gene of 10 Saudi patients from 8 families, no similar study was conducted in our region.

We describe the clinical, biochemical findings and the mutational analysis of 10 Saudi patients from 8 families. Molecular testing was performed on genomic DNA isolated from peripheral leucocytes. PCR and direct Sanger sequencing of all exons of SRD5A2 gene were performed.

At birth 70% of the patients were raised as girls based on the appearance of the external genitalia. 3 of them (43%) reassigned to boys after the diagnosis. 40% of the patients have microphalus with hypospadias. T/DHT when done was high in all of them except one. Molecular data revealed different mutations most of them harbor homozygous missense mutations.

In this paper we have confirmed the variability of the clinical picture among the patients with 5 alpha reductase deficiencies with predominance of female external genitalia. No phenotype/ genotype relationship could be determined.

PROGRESS: Ongoing.

PROJECT TITLE: Cystic Fibrosis Related Diabetes

INVESTIGATORS: *Afaf AlSagheir, Hanaa Banjar, Sara AlBanyan*

ABSTRACT: Cystic Fibrosis-related Diabetes (CFRD) is the most common co-morbidity in association with cystic fibrosis. Cystic fibrosis related diabetes is predominantly an insulin deficiency state it shares features of both Type 1 and Type 2 diabetes, yet there are important differences, which necessitate a unique approach to diagnosis and management. Development of Cystic fibrosis related diabetes is associated with a worse lung function, poorer nutritional status, and more chest infections.

This is a retrospective study at KFSH&RC 300 Cystic fibrosis patients were reviewed including 173 females, and 127 males.

At KFSH&RC 300 Cystic fibrosis patients were reviewed including 173 females (58%), and 127 males (42%). 35 (12%) patients had CFRD, 12 males (9%), 23 females (13%). 64% had developed DM before the age of 15 years.

Oral Glucose Tolerance test OGTT was performed as a screening test in patients above the age of 10 years. The majority of tests were done in the years of 2014 and 2015 including 26 (8.6%) patients. 9 (34%) patients had CFRD, 9 (34%) had impaired glucose tolerance, 8 (31%) had normal glucose tolerance.

CFRD appeared to be more common in females than males. The onset of CFRD is very early in the studied population. Physicians started performing Oral Glucose tolerance test) OGTT) to screen Cystic fibrosis patients. One third of the population screened had CFRD. More studies need to be done to identify the incidence and the prevalence of CFRD among CF patients

PROJECT TITLE: Nutritional Data of Cystic Fibrosis Patients at KFSH&RC
RAC# 2151176

INVESTIGATORS: *Hanaa Banjar, Sharifa AlZafiri, Mohammed Banami, Sami AlHaider*

ABSTRACT: Growth failure and malnutrition are well documented to have unfavorable prognostic factor in cystic fibrosis patients. There is clear association between malnutrition and deterioration in lung function in.

OBJECTIVES: To evaluate the current growth and nutritional status of CF patients at KFSH&RC in Saudi Arabia, and to review the impact of growth failure and nutritional status on the patient's morbidity and mortality.

A retrospective chart review of 229 cystic fibrosis patients in KFSH&RC for nutritional data which included: Percentile for weight and height, Body mass Index (BMI) and Z-score for weight and height.

Of 229 CF patients, 38% were diagnosed under age one year and the mean period of follow up 7.02 years. More than 60% of patients were found to be in mild-moderate malnutrition level at presentation. Z-score improved only in the first 6-12 months after oral rehabilitation, but plateaued thereafter.

The mean Z-score at first OPD visit was (-2.1) for height and (-1.6) for weight compared to the mean z-score of (-1.4) for height and (2.02) for weight at last visit. Around 40 % of patients are below 5th percentile for weight and 23% for height at last follow up visit.

With longer follow up period, the nutritional data deteriorate due to progressive lung disease. Early Nutritional rehabilitation with NGT or GT feeding should be established. Further study is needed to construct a specific CF growth chart at KFSH&RC.

PROJECT TITLE: Vitamin E & A & K Deficiency in Cystic Fibrosis Patients at KFSH&RC.
RAC# 2151 170

INVESTIGATORS: *Hanaa Banjar, Ali AlMehidib, Wajeeh Aldekhail, Maryam Dabour, Sami AlHaider, Ibrahim AlMogari*

ABSTRACT: Cystic fibrosis (CF) is the most common genetic disease occurring in Caucasians, of autosomal-recessive inheritance. It is a systemic disease, in the course of which pathologies of different systems and organs can be observed.

A retrospective study of Vitamin A, E and K levels in CF Patients using the RAC approved CF registry, which included demographic and laboratory data.

A total of 417 CF patients confirmed CF in our KFSH&RC registry, we retrospectively reviewed more than 200 patients of them for the results of the vitamins A, E and K levels during routine assessment.

Vit E deficiencies of < 5.5 mg/L were detected in (34%), Vitamin A deficiency of < 343 mcg/L was detected in (51.5%, Vit K deficiency of < 0.10 Nano gram/mL in (7.6%).

Vit A, E, K deficiency is common in CF Patients in our population. We recommend routine monitoring of their level in our center and early treatment before complications develop.

AIMS: The objective was to develop evidence-based clinical care guidelines for the screening, diagnosis, management, and treatment of vitamin E & A & K deficiency in individuals with cystic fibrosis (CF).

PROJECT TITLE: Intramural Esophageal Foreign Body in a Child

INVESTIGATORS: *Wajeeh AlDekhail, Chahdah Skaff, Haifa AlAwdhi*

ABSTRACT: Foreign body ingestion is a common problem in pediatric population. The majority occur between 6 months and 3 years of age. Major complications as bowel perforation and obstruction have been reported. 40% of ingested foreign bodies are unwitnessed, in fact many are asymptomatic.

We are reporting a case of 2 year old girl who was referred to King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia (KFSH&RC) suspected congenital esophageal stenosis. Upon investigation, she ended up as a case of intramural esophageal foreign body.

The family was interviewed for clinical history. The reports from the referral hospital were reviewed. The patient's hospital records were reviewed electronically as well as the paper based file. The recorded operation was seen after taking the permission of the family and surgeon.

The patient was investigated thoroughly after the second dilatation, to rule out cartilaginous ring. Ct scan was done and showed intramural foreign body. An urgent surgery was done to remove it. The foreign body was identified as aluminum can cover. The child tolerated the procedure well and was discharged on day 6 post operation.

Intramural foreign bodies are possible serious conditions that might be masked by unusual symptoms. There should be a high index of suspicion for this possibility for all pediatrics patients who present with long-standing, unexplained dysphagia.

PROJECT TITLE: Vitamin D Deficiency in Cystic Fibrosis Patients at KFSH&RC
RAC# 2151171

INVESTIGATORS: *Hanaa Banjar, Ali AlMehaidib, Abdulhakeem AlMuhndus, Afaf AlSagheir, Ibrahim Al-Mogarri, Sami Al-Haider,*

ABSTRACT: Cystic fibrosis (CF) is the most common genetic disease occurring in Caucasians, of autosomal-recessive inheritance. It is a systemic disease, in the course of which pathologies of different systems and organs can be observed.

Patients with cystic fibrosis (CF) are at risk of developing low bone mineral density (BMD) and fragility fractures.

It is now widely recognized that people with cystic fibrosis (CF) are at increased risk of developing low bone mineral density (BMD) and sustaining a low trauma fracture. The purpose of this Euro Care CF-funded work package was to develop consensus statements that (a) summaries current knowledge of the epidemiology and pathophysiology of CF-

related low BMD and (b) provide guidance on its assessment, prevention and treatment.

This study to evaluate our cystic fibrosis (CF) for metabolic disease.

AIMS: The objective was to develop evidence-based clinical care guidelines for the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis (CF).

PROJECT TITLE: Breaking Bad News in Children with Chronic Kidney Disease: Questionnaire Based study
RAC# 2151142

INVESTIGATORS: *Turki AlShreef, Weam AlMiman, Areej AlFattani*

ABSTRACT: Breaking bad news to parents whose children with chronic kidney disease (CKD) is an important role of nephrologists. In our practice we noticed that there has been a thought of parental dissatisfaction with how they were informed about their child's condition. Saudi parents preferences for how to be told the bad news about their child's CKD has not been investigated adequately.

A cross sectional study was conducted, parents or caregivers of 61 Pediatric patients who has CKD answered a questionnaire regarding their preferences

of how they wish the news were delivered to them and what was the dissatisfaction issues at that time when they got the news. The study was conducted in the outpatient clinics, peritoneal dialysis and in the hemodialysis area at KFSH&RC over 3 months period. Main outcomes were recorded in the questionnaire were: general emotional satisfaction and knowledge satisfaction in breaking bad news to caregivers of pediatric CKD patients.

61 patients with age (1-14) years, mean age of 8.3 years. Around half 53.8% of the caregivers were having university education. While 41.5% of them have general education. Only 1.5% of the caregivers were illiterate.

49% of the families undergo high income >16000 SR per month. 22.4% were earning less than 11000 SR monthly. Families who earn between 13000 – 16000 SR per month were around 14.3%, which are similar to those who have monthly income between 11000 – 12999 SR.

The Saudi population is very satisfied emotionally more than the satisfaction about the amount of information that they got. Different demographic data can affect their preferences in the way that they receive the bad news.

AIMS: The objective of this study is to identify the background idea about breaking bad news in the general Saudi population whose children have CKD, Studied different factors in term of level of education, socioeconomic level and geographical variations and their preferences of how much information they want to get. Knowledge about parent's satisfaction in breaking bad news can facilitate a change in the communication skills of the doctors and patients, and ultimately can improve the psychological quality of patients and their families and the quality of their life.

PROJECT TITLE: Galactosemia: A Single Center Experience in Saudi Arabia
RAC# 2151045

INVESTIGATORS: *Wajeeh AlDekhail, Maimonah Alfaheed, Ali Al-Mehaidib, Khalid Al-Saleem, Mohammed Banemai, Abdulrahman Al-Khateeb*

ABSTRACT: Galactosemia (Omim # 230400) is an autosomal recessive disorder of galactose metabolism caused by mutation in galactose1-phosphate uridyl transferase (GALT) occurs in approximately 1 of 60,000 live births.

The newborn who received high amount of lactose in the breast milk or certain formulas without the transferase enzyme will be unable to metabolize galactose-1-phosphate which will accumulated in the body leading to complication including liver failure, increase risk of gram negative infection, jaundice, vomiting, diarrhea and cataract.

Early diagnosis and treatment have improved the prognosis of galactosemia and dietary restriction of galactose is lifesaving in the neonate. However the long term complications present even in dietary restriction include neurological, cognitive disorder and osteopenia.

This was a retrospective, descriptive study for data collected from Jan. 1980 to Dec. 2014 for patients diagnosed KFSH&RC OR other hospital and referred for follow up and treatment.

14 patients diagnosed with galactosemia 10 of them are male. the main presentation were hypoglycemia 92.9%, lethargy85% and 71% of patients had liver dysfunction. Incidence of gram negative infection is 46%.cataract was seen in 78% and developmental delay including speech and cognitive function 35%.44% of patients

were diagnosed by newborn screening test and approved by genetics test.

The male more affected than female and liver dysfunction improved with galactose restriction diet, there was a very high percentage of cataract in comparison to other case series and 47% of patients with cataract had mutation in S135L and some of patients required surgical intervention

PROJECT TITLE: Cystic Fibrosis (CF) Registry
RAC# 2111016

INVESTIGATORS: *Hanaa Banjar, Ibrahim Al-Mogarri, Sami Al-Haider, Talal Al-Maghamsi, Imran Nizami, Edward Devol, Bader ALHablani, Manal AlShaikh*

BACKGROUND: The incidence of CF in Saudi Arabia (SA) was reported to be 1 in 4243 live birth. Demographic and genetic data was described before in SA and the Gulf area. The mean survival in most Arab coutries10-20 years due to delayed diagnosis, delayed treatment and poor compliance to medications.

The CF care in SA is scattered between different hospitals, and median survival differs from one hospital to another as well as from one Gulf country to another due to difference in medical care, availability of medications and difference in CFTR mutations, in addition to consanguinity between certain families.

AIMS

- To obtain the incidence, prevalence and patterns of CF diseases in KFSH&RC and later in the Kingdom of Saudi Arabia.
- To identify the risk factors associated with CF diseases
- To document the treatment procedures and assessment of treatment outcome.

PROGRESS: Ongoing.

PROJECT TITLE: Establishment of Primary Immunodeficiency Disease (PID) Registry at KFSH&RC
RAC # 2081111

INVESTIGATORS: *Bander Al Saud, Saleh Al Mohsin, Abdulaziz Al-Ghonaium, Hamoud Al-Mousa, Hasan Al-Dhekri, Hassan Al-Rayes, Amal Al Seraihy, Rand Arnaout, Sulaiman Al-Gazlan, Jawad Afzal, Nazeema Elsayed*

BACKGROUND: Primary immunodeficiency disorders (PID) reflects abnormalities in the development and maturation of cells of the immune system. These defects result in an increased susceptibility to recurrent infections, autoimmune disease, and malignancy. They are very heterogeneous group of disorders in their clinical presentations and underlying pathophysiology. The underling immunopathology affect distinct components of the immune system, such as neutrophils, macrophages, dendritic cells, complement proteins, natural killer cells, T and B lymphocytes. So far more than 120 genes are identified, whose abnormalities account for more than 150 different phenotypes of PID. These PID diseases are classified in to 8 main categories:

- Combined T and B cell immunodeficiency
- Predominately antibody immunodeficiency
- Other well-defined immunodeficiency
- Disease of immune dysregulation
- Congenital defects of phagocyte number, function, or both
- Defects in innate immunity
- Auto inflammatory disorder
- Complement deficiencies

To determine the magnitude and types of PID diseases encountered in our population at King Faisal Specialist Hospital and Research Centre

(KFSH&RC), we design and established a PID registry for all patients seen at our hospital. Upon successful data collection other health care centers in the country will be added, to have national representation of the registry.

PROGRESS: Ongoing.

- A total of 711 patients have been registered so far.
- Continuous Data Acquisition
- Continuous Data Validation
- Continuous Data Auditing

PROJECT TITLE: Efficacy of Prophylactic Glycerin Suppositories for Feeding Intolerance in Very Low Birth Weight Preterm Infants; A Randomized Trial
RAC # 2121110

INVESTIGATORS: *Emad Khadawardi, Jasim Anabrees, Eyad Al-Midani, Khalid Al-Faleh*

AIMS: To evaluate the efficacy of prophylactic glycerin suppositories will accelerate the elimination of meconium from the large intestine and thus reduce the incidence of feeding intolerance in very low birth weight (VLBW) infants.

PROGRESS: Ongoing.

- 108 cases were recruited in total.
- 59 cases are from KFSH&RC.
- 49 cases are recruited from Al Habib Hospital.
- No observed side effects on the Intervention Group.
- No major complications observed.

PROJECT TITLE: Development of Population-based Newborn Screening for Severe Primary Immunodeficiency Diseases in Saudi Arabia
RAC# 2130027

INVESTIGATORS: *Hamoud Al-Mousa, Abbas Hawwari, Majed Dasouki,*

AIMS

- Develop and adopt a combined TREC & KREC assay using real time qPCR.
- Determine TREC & KREC number in gDNA from patients known to have various immune deficiency syndromes including: SCID, T cell lymphopenias, T or B-cell defects, and DOCK8 mutation positive autosomal recessive Hyper IgE syndrome.
- Validate the TREC & KREC assay in gDNA from anonymous dried blood spots (DBS) collected routinely for newborn screening from full term and premature newborns.
- Mutation screening of gDNA from all samples with abnormal TRECs &/or KRECs number using the newly designed "Ion Ampliseq Primary Immune Deficiency Gene Panel" followed by validation of potentially pathogenic DNA variants using Sanger sequencing.
- Calculate the incidence of SCID, B-cell defects in the screened population.

PROGRESS: Ongoing.

PROJECT TITLE: Underlying Molecular Genetic Defects of Primary Immunodeficiency Diseases in Saudi Arabia
RAC# 2080025

INVESTIGATORS: *Hamoud Al-Mousa, Anas Alazami, Abdulaziz Al-Ghonaium, Hasan Al-Dhekri, Saleh Al-Muhsen, Rand Arnaout, Bandar Al-Saud, Dorata Monies,*

AIMS

- Assessment of primary immunodeficiency patients seen in KFSH&RC based on medical records/laboratory findings and clinical presentation. Cases will be Classified based upon:

a. Medical record review including hereditary family history; and
b. Medical records review and available family history of deceased cases.

- Enrollment of index cases and their family members according to family history and laboratory findings. Retrospective and Prospective cases will be enrolled.
  a. Retrospective DNA samples that are derived from deceased patients will be anonymized (unless informed consent is granted by a guardian).
  b. Pre/post bone marrow transplant (BMT) samples derived from current Primary Immunodeficiency patients. Consented skin fibroblasts, saliva or buccal cells, will be collected from patients when pre-BMT samples are not available.
  c. Prospectively up to 100-200 new cases (3-5 per month) are expected.
- Carry out candidate gene studies: SNP and microsatellite genotyping and heliotyping of samples with focus on markers within or near the genes followed by sequencing when applicable.
- Conduct expression and linkage analysis, using Affymetrix GeneChip® Mapping 250K chips or equivalent, on pedigrees when loci linked to known genes are excluded and sufficient statistical power is present for achieving LOD scores >2.
- Identification and characterization of novel genes responsible for Primary Immunodeficiency disorders.

PROGRESS: Ongoing.

PROJECT TITLE: Improving Medication Reconciliation Compliance at Admission: A Single Department's Experience

INVESTIGATORS: *Eyad Almidani, Emad Khadawardi, Turki Alshareef, Ibrahim Bin Hussain, Saleh Almofada, Ann Joo Ham, Abdulaziz Alqarni, Rania Alobari, Maria Cecilia Bernardo, Mohammad Hasan Rajab*

ABSTRACT: Most previous efforts at our institution to revamp the medication reconciliation process have failed. Thus, we used an innovative evidence-based approach to improve compliance with the reconciliation process at admission. This approach focused on the Department of Pediatrics at King Faisal Specialist Hospital and Research Center. We established specific educational and monitoring programs to run over a 2 months period of time from June 2015 till the end of July 2015.

The date collected from this study will be electronically entered into a database. The departments from research center biostatistics, epidemiology and scientific computing (BESC) will carry out statistical analysis of the data utilizing the appropriate techniques. We hope to achieve all these activate in a period of 6 months.

This is a retrospective study which will utilize existing information, with no additional blood test or any other procedure used for purpose of the study.

AIMS: To improve the compliance with medication reconciliation process at the time of patient admission in the department of pediatrics at King Faisal Specialist Hospital and Research Center, Riyadh, Kingdom of Saudi Arabia using an innovative evidence-based approach.

PROJECT TITLE: Effect of Mobile Phone Short Text Messages on Glycemic Control in Type 1 Diabetic Children

RAC # 2141120

INVESTIGATOR: *Bassam Bin-Abbas*

ABSTRACT: Optimal diabetes care and management involves considerable behavioral modification, and non-adherence to therapy contributes significantly to poor glycemic control1. Extensive research on psychological interventions aiming to improve glycemia suggests that current strategies are costly and time-consuming especially in children and adolescents with type 1 diabetes 2,3. Mobile phone text messaging has rapidly become a socially popular form of communication. It is personal, highly transportable, and widely used, particularly in the Western countries 4-7. However, text messaging coupled with specific behavioral health strategies has yet to be utilized effectively in developing countries with high prevalence of diabetes. Several papers showed mobile phone may offer a means of contact and support between clinic visits and may increase adherence with insulin therapy regimens and improve clinical outcome 8-10.

AIMS: To test the feasibility of a telemedical educational support program using phone short message service (SMS) and to evaluate its effect on glycemic control in children with type 1 diabetes.

PROGRESS: Ongoing.

PROJECT TITLE: International Pediatric Fungal Network (PFN) Registry. Multi-Center Studies to Improve Diagnosis and Treatment to Pediatric Candidiasis
RAC # 2091044

INVESTIGATORS: *Ibrahim Bin-Hussain, Asim Belgaumi, Sahar Thawadi, Suliman Al Jumaah, Sami Al Hajjar, Haysam Tufenkeji, Husn H. Frayha, Fahad Al Hazzani, Manal Al Shike, Jihan Hassanein, Kris Ann Hervera, Ohoud Al-Yabes*

BACKGROUND: The International Pediatric Fungal Network (PFN) is undergoing an exciting transition with the new NIH R01 funding. The new PFN will contain two coordinating centers: Duke University (led by Bill Steinbach) will serve as the Database Coordinating Center, and the Children's Hospital of Philadelphia (CHOP; led by Theo Zaoutis) will now serve as the Regulatory Coordinating Center.

The revised PFN project, referred to as PFN-R01 Candidiasis, is a study that builds on the previous PFN epidemiology work. The overall goal of the PFN-R01 Candidiasis study is to develop evidence-based treatment guidelines for invasive candidiasis in children through the largest, multi-center, multi-national comparative effectiveness study of pediatric invasive candidiasis.

The NIH R01 funding is to utilize a comparative effectiveness strategy to define the optimal treatment for pediatric invasive candidiasis. While the PFN database contained patient information on a range of invasive fungal infections, this current study will focus exclusively on pediatric invasive candidiasis.

AIMS: The overall objective of this protocol is to:

- Compare the effectiveness of echinocandin versus amphotericin B or triazole antifungal therapy for pediatric invasive candidiasis; and
- Define the incidence of pediatric candidiasis.

PROGRESS: Ongoing.

PROJECT TITLE: Cyclophosphamide use in Juvenile Systemic Lupus Erythematosus (JSLE) in a tertiary care center in Saudi Arabia, A Retrospective Study
RAC # 2081048

INVESTIGATORS: *Abdullah AlSonbul, Suliman AlMayouf, Abdullah Nour, Naser Ahmed*

AIMS: Looking at our tertiary center experience with cyclophosphamide treatment in children with systemic lupus erythematosus (SLE) especially in terms of safety and efficacy.

PROGRESS: Ongoing.

A total of 71 patients received Cyclophosphamide, 61 were females (86%). The mean age of disease onset, disease diagnosis, and cyclophosphamide initiation was 9.2, 9.6, and 10.4 years respectively. Mean duration of follow-up was 6.6 years. Nephritis (49.3%) then cerebritis (18.3%) were the main indications. Comparisons of SLEDAI and SLICC of the whole cohort pre and post treatment were statistically significant with p-values of 0.001 and 0.006 respectively. No statistical significant difference was found after comparing SLEDAI and SLICC scores after 6^{th} & 12^{th} doses.

49 patients (69%) had no major side-effects. Major side effects encountered included: 7 patients had herpes zoster infection (10%), 3 had significant alopecia (4.2%), 2 had skin abscesses in 2, 1 had recurrent lung abscesses, 1 had recurrent urinary tract infection, and 1 had allergy to means.

Cyclophosphamide is still considered important effective treatment in severe JSLE. It is relatively well tolerated among children however infections remains a major infrequent problem so shorter course is recommended.

PROJECT TITLE: Invasive Pneumococcal disease (IPD) in Hospitalized Children: Disease Burden and Serotypes Distributions
RAC# 2121105

INVESTIGATORS: *Sami Al Hajjar, Faisal Al Aklabi, Ibrahim Bin-Hussain, Sahar Al-Thawadi*

AIMS

- Describes the epidemiology and serotype distribution of IPD in hospitalized children
- Describes the outcome of IPD, including special high-risk populations
- Evaluate reasons behind failure in conjugated pneumococcal vaccine: Failure to vaccinate or failure of vaccine

PROGRESS: Ongoing.

PROJECT TITLE: Prevalence of Atypical Bacterial Pathogens in Community Acquired Pneumonia Among Children at Tertiary Care Hospital
RAC#2121104

INVESTIGATORS: *Sami AlHajjar, Ibrahim BinHussain, Shaikha AlDossary, Mohammed Shoukri*

AIMS: Prevalence of atypical Bacterial Pathogens in community Acquired pneumonia among children at Tertiary care hospital (KFSH&RC).

PROGRESS: Ongoing.

PROJECT TITLE: Human BOCAVIRUS (HBOV) in High-risk Children
RAC# 2151140

INVESTIGATORS: *Sami AlHajjar, Ibrahim BinHussain, Shaikha AlDossary, Mohammed Shoukri*

BACKGROUND: Baca virus is a single- standard DNA virus belonging to the family parvoviridae, subfamily parvirinae, genus Boca virus. Human Boca virus (HBoV) was first reported in Swedish Children's with acute respiratory tract infections in 2005It was subsequently detected in children with respiratory

tract infections in addition to gastroenteritis worldwide. HBoV has been reported in various countries, indicating its worldwide endemic nature. The prevalence of HBoV ranges between 1.5 to 19.3%.

AIMS: The role of HBov as a pathogen in human infection is further confounded by simultaneous detection of other viral pathogens in patients from whom HBov is identified, with co- infection rates as high as 80%.

This study was investigating the total burden of human Boca virus (HBoV) among high – risk (HR) children who have chronic medical conditions or are immunocompromised and hospitalized with acute respiratory tract infection.

PROGRESS: Ongoing.

PROJECT TITLE: Allergic Bronchopulmonary Aspergillosis in Children with Cystic Fibrosis in Saudi Arabia: A Single Center Experience
RAC# 2151173

INVESTIGATORS: *Sami AlHaider, Ibrahim AlMogarri, Hanaa Banjar, Ahmad Yousif Qudair*

BACKGROUND: Cystic Fibrosis (CF) is a chronic disease with multisystem involvement due to an inherited defect in the cystic fibrosis transmembrane conductance regulator (CFTR) protein.[1] Lung disease is among the commonest manifestations of this disorder and accounts for 80% of mortalities. [2] Allergic bronchopulmonary aspergillosis (ABPA), on the other hand is a disorders that results from a hypersensitivity reaction to the fungus, and mainly affects asthmatic individuals and patients with CF.[3] Recent studies indicated variable prevelance of ABPA among CF patients ranging between 1% to 14%.[4] The occurrence of ABPA in CF patients may lead to worsening prognosis making early diagnosis and management essential.[5] King Faisal Specialist Hospital & Research Centre (KFSH&RC) is the leading referral CF center in the region with >200 patients population. The aim of this study is to provide a local data concerning the relationship between CF and ABPA in Saudi Arabia.

AIMS

- Review of clinical presentation, radiological and laboratory findings of ABPA in CF children followed in KFSH&RC, Riyadh.
- The following risk factors will be assessed: age, gender, body mass index (BMI), atopy, inhaled or systemic antibiotics, inhaled corticosteroid (ICS), azithromycin, Pseudomonas, vitamin D, and geographical distribution.

PROGRESS: Ongoing.

PROJECT TITLE: Utility of Serum Ferritin as a Marker of Disease Activity in Childhood Systemic Lupus Erythematosus.
RAC# 2151210

INVESTIGATORS: *Sulaiman M Al-Mayouf, Alwaleed Aljaser, Nora Almutairi, Manal AlShaikh*

BACKGROUND: Ferritin is an intracellular protein that functions principally as iron storage medium and releases it in a controlled fashion, yet it also has a dual function as an acute phase reactant that is elevated in various autoimmune disorders, Ferritin may play a direct role on the immune system, it has been positively correlated with disease activity scores of various autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis. However, similar findings are limited in childhood lupus populations. In this study, we will determine if elevated levels of ferritin in childhood lupus patients correlate with disease activity and organ involvement.

AIMS

- To assess the usefulness of serum ferritin levels as a marker of disease activity and organ involvement in Saudi childhood SLE cohort
- To screen children with SLE for subclinical macrophage activation syndrome.

PROGRESS: Ongoing.

PROJECT TITLE: Rapid Shallow Breathing Index as a Predictor Factor of Successful Extubating in Neonates
RAC# 2151165

INVESTIGATORS: *Saleh AlAlaiyan, Faisal Khan, Mohammed AlJabr, Ali AlMasallam, Fahad AlHazzani*

ABSTRACT: The decision to extubate infants is usually based on clinical assessment, blood gases, and ventilator settings which is very subjective and failure to sustain extubation more than 72 hours is high.

Failure of early extubation in premature infants is due to poor respiratory drive, atelectasis, residual pulmonary function abnormalities or intercurrent illness.Failure of extubation in infants who have prolonged endotracheal intubation is uusually due to bacterial colonization, sepsis, subglottic injury, and bronchopulmonary dysplasia. Studies in neonates that examined the usefulness of rapid shallow breathing index on ET-CPAP are limited. However, some of these studies confirmed high sensitivity, specificity, positive and negative predictive tests.

In this study, we would like to evaluate the rapid shallow breathing index on endotracheal tube-spontaneous breathing (ET-SB) in neonates, as a predictor of successful extubation.

PROGRESS: Ongoing.

PROJECT TITLE: Elucidation of Ion Transport Defects in Congenital Diarrhea
RAC# 2151042

INVESTIGATORS: *Khalid AlSaleem, Ali AlMehaidib*

BACKGROUND: Congenital diarrhea like Microvillus Inclusion Disease (MVID) and Congenital Chloride Diarrhea (CCD) both are rare diseases worldwide but more common in Saudi Arabia and the Middle East. The diseases cause severe diarrhea that can lead to dehydration and death in newborn infants and children. There is no treatment for MVID and treatment for CCD is not definitive. The cause of the severe diarrhea is unknown.

Microvillus Inclusion Disease MVID is a rare disease worldwide but more common in Saudi Arabia and the Middle East. The disease causes severe diarrhea that can lead to dehydration and death in newborn infants and children. There is no treatment for MVID. In order to survive, infants and children with MVID require continuous support with intravenous parenteral nutrition. If bowel transplantation is available, some patients can survive following transplantation. The cause of the severe diarrhea is unknown.

AIMS: We are studying intestinal tissues from patients with congenital diarrhea i.e. Microvillus Inclusion Disease to understand the reason that affected patients develop severe diarrhea.

By studing the alterations in the proteins that control fluid secretion in the intestine of patients we can use the knowledge to develop therapeutic drugs to treat both diseses.

PROGRESS: Ongoing.

PROJECT TITLE: Congenital Glucose-Galactose Malabsorbtion: Single Center Experience.
RAC# 2141143

INVESTIGATORS: *Khalid AlSaleem, Yasie AlSuyufi, Ali AlMehaidib, Mohammed Banemai, Wajeeh AlDekhail, Faiqa Imtiaz, Rabab Allam*

BACKGROUND: Congenital Glucose-Galactose Malabsorbtion (CGGM, OMIM# 606824) is an autosomal recessive disorder, first described in 1962 that usually presents in newborn with sever galactose in the intestine. This disorder arises due to a defect in the sodium- dependent glucose co-transporter (SGLT1, a membrane protein that normally transports these monosaccharides across the intestinal brush-border. If not diagnosed and treated early, this condition is life threatening and can be resolved by preventing diarrhea with an elimination of glucose and galactose from the diet. One the crucial dietary modification is effective; patients usually recover and develop normally.

AIMS

- To retrospectively, review the clinical data for all of the pediatric CGGM cases (less than 14 Years of age) that have been diagnosed at King Faisal Specialist Hospital & Research Center, Riyadh (from January 1994 to July 2014)
- To Prospectively, obtain full informed consent from CGGM affected patients and available affected/ unaffected family members to withdraw a whole blood sample for genomic DNA extraction. DNA extracted will be subjected to direct Sangar sequencing and subsequent mutation analysis for the coding and intron/ exon boundaries for the SLC5A1 gene.

PROGRESS: Ongoing.

PROJECT TITLE: Endoscopic Retrograde Cholangiopancreatograpy (ERCP) Experience Among Pediatric Patients in KFSH&RC
RAC# 2141073

INVESTIGATORS: *Khalid AlSaleem, Haifa AlAwadhi, Ali AlMehaidib, Mohammed Banemai, Wajeeh AlDekhail*

BACKGROUND: ERCP has been largely implicated in the treatment of pancereatico- biliary disease among adults. However, its use is still not well established among pediatrics patients. Reports, from all over the world and particularly from Saudi Arabia, are limited. Furthermore, guidelines for use of ERCP in pPediatrics are still not established.

AIMS

- Identify the most common indication for ERCP in KFSH&RC.
- Assess the indications, findings, therapies, safety, effect on management and complications related to ERCP in our hospital's Pediatrics population.
- Compare our experience to other local institutions experience and to international experience.

PROGRESS: Ongoing.

PROJECT TITLE: Nephropathic Cystinosis the experience in Saudi Arabia
RAC# 2151050

INVESTIGATORS: *Essam AlSabban, AlHanouf AlSaleem*

BACKGROUND: Cystinosis is an autosomal recessive disease characterized by the intralysosomal accumulation of cysteine, as a result of a defect in cysteine transport across the lysosomal

membrane, with an incidence of 0.5-1.0 per 100 000 live birth 3.

Cystinosis is caused by CTNS gene mutation (17p13.2) that encodes lysosomal cysteine transporter cystinosin. To date, more than 100 mutations were identified, 76% are caused by large deletions of 57KB(1,3)

Cystinosin is a 367 amino acid protein functioning as lysosomal cysteine out of the cells, when it is mutated; cysteine will be accumulating and crystallizing in the lysosomal cells, leading to abnormal cellular function and specific deformity in the proximal tubules known as swan neck deformity, explained as non- functioning atrophic segments of the tubules.

In clinical practice the diagnosis of cystinosis can be established by having at least one of the following tests: High levels of leukocyte cysteine, confirmed corneal cysteine crystals by slit lamp examination, and genetic analysis.

AIMS: Review our experience with regard to : patient demography, age at the diagnosis, biochemical data, clinical outcome and reported gene mutations. This would be the first comprehensive regional study on patient with cystinosis.

PROGRESS: Ongoing.

PROJECT TITLE: Gastrointestinal Manifestation in Children with Sanjad Sakati Syndrome
RAC# 2151021

INVESTIGATORS: *Wajeeh AlDekhail, Halima Jowder, Ali AlMehaidib, Afaf AlSagheir,Sharifa AlZafiri*

ABSTRACT: Sanjad Sakati Syndrome (SSS) or hypoparathyroidism–retardation-dysmorphism is rare disorder with clinical picture of delay of growth and development, mental retardation and dysmorphic features.

AIMS: In this study we will describe the gastrointestinal manifestation of patients with SSS who were referred to King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

PROGRESS: Ongoing.

PROJECT TITLE: Congenital Hepatic Fibrosis, A Single Centre Experience
RAC# 2141119

INVESTIGATORS: *Wajeeh AlDekhail, Ali AlMehaidib, Khalid AlSaleem, Mohammed Banemai, Haifa AlAwadhi, Ayman Mohammed, Abdulrhman AlKhateeb*

ABSTRACT: Congenital hepatic fibrosis (CHF) is a rare, autosomal recessive, multi-systemic, fibropolycystic disease with no well-known causes identified yet. CHF is known for its variable presentations and is commonly associated with autosomal recessive polycystic kidney disease (ARPKD). Despite its rare nature, a big number of cases were identified and managed at KFSH&RC over the past 25 years. This gives us the opportunity to explore the characteristics of these co-existing conditions and how they relate like never before. This is especially true as we explore their geno-phenotype relationship for the first time ever. This will significantly contribute to the understanding of these rare co-existing conditions in addition to setting solid bases that can be later used for the development of the best approaches for their identification and management.

AIMS: We aim to thoroughly characterize the relationship of the genotypes, phenotypes, risk factors, associations, prognostic factors, complications, management strategies and long-term outcomes of this rare disease through the study of the CHF children population managed at KFSH&RC over the past 25 years. We further aim to explore how these elements are different specificity in CHF affected children associated with ARPKD in comparison to other reported patient populations as we hypothesize to find significant differences due to the high consanguinity rates among our community.

PROGRESS: Ongoing.

PROJECT TITLE: HLA Association with Primary Immunodeficiency Disease and its Impact on Transplantation Outcome
RAC# 2151132

INVESTIGATORS: *Hasan AlDhekri, Abdulaziz AlGhonaim, Saleh AlMohsen, Bashayer alrasheed, Sahar Shorbaji, Bander AlSaud, Homoud AlMousa, Rand Arnaout, Mouhab AlAwami*

BACKGROUND: The Human leukocyte Antigen (HLA) system is located in the major histocompatibility complex (MHC) in humans on the short arm of chromosome 6. The HLA region is the most polymorphic region in the human genome and it is divided into three classes: HLA class I, class II and class III genes.

HLA genes being highly polymorphic are present in multiple alleles that are co-dominantly expressed on the cell surface.Since the HLA genes are closely linked genes, they are transmitted from parents to offspring as blocks of HLA alleles called haplotype, the HLA allele and haplotype have very important applications in different fileds including solid organ or hematopoietic stem cell transplantation and dissese association, in transplantation biology, the HLA molecules are very immunogenic and are the major barrier to transplantation.

AIMS: To review the HLA haplotypes of all primary immunodeficiency (PID) patients followed up in KFSH&RC and discuss their association and the impact of haplotypes on transplantation outcome.

PROGRESS: Ongoing.

PROJECT TITLE: Hematopoietic Stem Cell Transplantation for Primary Immunodeficiency Disease Single Center Experience
RAC# 2151103

INVESTIGATORS: *Hasan AlDhekri, Abdulaziz AlGhonaim, Saleh AlMohsen, Bashayer alrasheed, Sahar Shorbaji, Bander AlSaud, Homoud AlMousa, Rand Arnaout, Mouhab Ayas, Amal AlSeraihy.*

AIMS: To review the King Faisal specialist Hospital and Research Center experience of all Primary Immunodeficiency (PID) patients who underwent Hematopoietic stem cell transplantation (HCT) from 1993-2014 and discuss the impact of different variable on transplantation outcome including the disease type, conditioning regimen, HLA typing, donor type, GVHD, bone marrow recovery and chimerism.

PROGRESS: Ongoing.

PROJECT TITLE: NK Cells impact on Hematopoietic Cell Transplantation Outcome for Severe Combined Immunodeficiency
RAC# 2151102

INVESTIGATORS: *Hasan AlDhekri, Abdulaziz AlGhonaim, Saleh AlMohsen, Bashayer alrasheed, Sahar Shorbaji, Bander AlSaud, Homoud AlMousa, Rand Arnaout, Ali AlAhmari, Mouhab Ayas*

AIMS: To review the King Faisal specialist Hospital and Research Center experience in (HCT) in SCID patient's from 1993-2014 and discuss the impact of host NK cell on transplantation outcome.

PROGRESS: Ongoing.

PUBLICATIONS

FULL PAPERS: (PEER-REVIEWED PUBLICATIONS)

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POSTERS / ORAL PRESENTATION

- Bassam BinAbbas. Effect of Mobile Phone Short Text Messages on Glycemic Control in Type I Diabetic Children. PUB # 2150065. Oral Presentation in Arab Diabetes Medical Congress 25 April 2015.
- Eyad AlMidani, Ibrahim Bin Hussain, Saleh AlMofada, Mohammed Hijazi, Norah AlMalhooq, Rania AlObari, Sami AlHaider, Maria Cecillia Bernardo, Emad Khadawrdi. Effect of Implemnting A standardize process on the Quality of Discharge Summaries. PUB # 2150088. Oral Presentation for 3rd International conference on pediatrics, May 18–20,2015 at Texas, San Antonio, USA.
- Bassam Bin Abbas. Impact of Diabetes Education on Competence and Glycemic Control of Type-1 Diabetic Children Treated at Outpatient Clinic at King Faisal Specialist Hospital & Research Centre.. PUB # 2150173. Oral Presentation for 6th Global Diabetes Summit & Medicare Expo Dubai 2–4 November 2015.
- Ali AlMehaidib, Wajeeh AlDekhail, Adel AlShahrani, Khaled AlSaleem,Mohammed Banamai. Progressive Familial Intrahepatic Cholestasis at Tertiary care center in Saudi Arabia. PUB # 2150008. Oral Presentation for the 24th conference of the Asian Pacific Association for the study of the Liver (APASL), Istanbul, March 12–15, 2015.
- Hamoud Al-Mousa. Primary Immunodeficiency Disorders in the Middle East. PUB # 2150083. Oral Presentation in the 15th international conference of Jorden pediatric Society & the 20th congress union & Arab pediatric Societis 29 April–02 May 15,Amman,Jordan and Approved on 19 March 15.
- Wajeeh AlDekhail, Haifa Alawadhi, Ali AlMehaidb, Hamdy Amin Mulia, Khalid AlSaleem, Mohammed Banemai. Bone Mineral Densitometry (BMD) following Aluminum (AL) Chelation in Children on long term Parenteral Nutrition. PUB # 2150018. Poster Presentation for 9th Asia Pacific conference on clinical

Nutrition. APCCN 2015. 26–29 January 2015, Shangri-La Kuala Lumpur, Malaysia.

- Sulaiman Al-Mayouf. Familial Childhood Rheumatic Diseases: Association of LACC1 Mutation with Monogenic Form of Systemic Juvenile. PUB # 2150317. Oral Presentation in 1stAnnual International Congress of Genetics (ICG-2016) will be hold during April 25–28, 2016 in Dalian, China.
- Turki AlShareef, Zuhair Rahbeeni, Hazem Awad, Abdelmoneim Eldali. Incidence and Characteristics of chronic Kidney Disease in Methylmalonic Acidemia at KFSH&RC. PUB # 2150043. Poster Presentation for 2015 in Cape Town, South Africa on 13–17 March 2015.
- Duaa Al-Romaili, Wajeeh Al-Dekhail Ali Al-Mehaidib, Hamad Al-Suhaibani. Transjugular Intrahepatic Portosystemic Shunt (TIPSS) in Children. PUB # 2150019. Poster presentation for the 8th Research Day on 12 February 2015 at postgraduate Center Auditrium.
- Wajeeh Al-Dekhail, Haifa AlAwadhi, Ali Al-Mehaidib, Hamdi Mulia, Mohammed Banami, Khalid AlSaleem. Use of bone mineral densitometry following Aluminum Chelation in Children on long term parenteral nutrition. PUB # 2150057. Oral Presentation for 4th Annual Middle East congress on clinical Nutrition, March 5–7, 2015 at Ajman, UAE.
- Hamoud Al-Mousa. Targeted- Next Generation Sequencing for primery Immunodeficiency Disease. PUB # 2150117.Oral Presentation the 4th ASCID congress, African society for Immunodeficiency, 29–31 May 2015, Algeria & approved from ORA on 26 April 15.
- Tariq AlAyed, Sami Taha, Husn Frayha, Sami AlHaider. Lethal legionella infection in an immunocompromised child: first reported case in the middle east. PUB# 2150186, Case Report in pediatric respiratory Disease 13–15 Nov 20152015
- Sulaiman Al-Mayouf. Monogenic and multifactorial autoinflammatory diseases: Clinical and laboratory characterization in a pediatric Saudi population". PUB # 2150212. Oral Presentation in 8th International Congress of Familial Mediterranean Fever and Systemic Auto inflammatory Diseases 30 September–3 October, 2015. Dresden, Germany
- Hamoud Al-Mousa. Unbiased Targeted next generation sequencing molecular approach for primary immunodeficiency diseases. PUB # 2150225.Poster Presentation in 2nd International primary immunodeficiencies congress, 5–6 November 2015, Budapest, Hungary.

AWARDS

Doaa AlRomaili, Ali AlMehaidib, Hamad AlSuhaibani, Wajeeh AlDekhail. Transjugular Intrahepatic Portosystemic Shunt (TIPSS) in Children

- Awarded "Best Poster Presentation" in 8th KFSH&RC Residents' Research Day 2015

FUTURE PLANS

- Our long term goal is design better strategies to diagnose, prognosticate and improve the management of pediatrics in the kingdom of Saudi Arabia.
- Improve the quality of clinical care by developing new analytical methods for evaluating medical treatments and applying these methods to innovate approaches to pediatrics patient care.
- Promote advancement of health outcomes research in the care of pediatrics patients.
- Maintain the momentum of trainee involvement in research.
- Conduct local Clinical Trials in the field of Pediatrics.

DEPARTMENT OF SURGERY

DEPARTMENT OF SURGERY

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THE DEPARTMENT OF SURGERY AT KFSH&RC IS AMONG THE MOST highly regarded surgical services in the Kingdom of Saudi Arabia with a proud history of clinical and academic achievements. We are committed to delivering world class collaborative patient care, while advancing scientific research and training the surgical innovators for tomorrow.

It is the goal of the Department to expand the basic and translational research by ensuring that each section will have at least three active research projects every year in collaboration with Research Centre and to be recognized in an international setting for high caliber researches.

During the year of 2015, the Department of Surgery continued to conduct the Annual Research Day, and many other educational activities through workshops, international forums, and surgery training sessions.

At the end of 2015, the Department of Surgery has 23 publications, 29 abstracts presented individually and in collaboration with other Departments at KFSH&RC and Internationally. We completed and closed 5 projects and 11 new research studies started during 2015. Currently there are 15 RAC approved ongoing projects and few awaiting Office of Research Affairs approval. These projects included studies, either individually or in collaboration with other Departments, national and International institutions.

PROJECT TITLE: Number of Regional Negative Lymph Node Affects Survival in Rectal Cancer Patients Treated for Cure
RAC#: 2131 017

PRINCIPAL INVESTIGATOR: *Al-Wusaibie Ahmed*
CO-PRINCIPAL INVESTIGATOR: *Mohammed Mahfoudh, Abduljabbar Alaa, Ashari Luai, Alhomoud Samar, Alsanea Naser*

PROJECT DESCRIPTION: The state of lymph node involvement in rectal cancer is the most important prognostic factor after a complete mesorectal excision. Hence, assessment of lymph node metastasis is critical in the evaluation of rectal cancer patients. As a single positive lymph node is sufficient enough to upstage the disease.

Literature review showed that the minimal number of lymph node ranges from 6-21 for accurate staging of colorectal cancer. We studied a specific group of patients with rectal cancer who has negative radiological and pathological lymph nodes. To our knowledge no study assessed the impact of the numbers of lymph nodes with a negative radiological and pathological staging on survival in rectal cancer patients treated for cure. A total of 44 patients were included between 2001 and 2011. A 5 years survival will be assessed at different level of lymph nodes.

PROGRESS: The study is in data analysis phase.

COLLABORATORS: Nasser Al-Sanea, MD, Colorectal Unit, Department of Surgery

PROJECT TITLE: Phyllodes Breast Tumors: KFSH&RC Experience
RAC#: 2131008

PRINCIPAL INVESTIGATOR: *Dr. Yousef Al-Alalawi, MD*
CO-PRINCIPAL INVESTIGATOR: *Osama Al-Malik,MD, Dr.Ihab Anwar, MD, Asma Tulbah,MD, Taher Twegieri*

PROJECT DESCRIPTION: Phyllodes tumors are uncommon fibroepitheliel brease tumors that capable a verse range of biologic behavior. In account for 0.3-1% of all breast tumors in females.

This is a retrospective study of 34 women with phyllodes tumors who were managed at our Hospital between 2000 and 2012. All available clinical, radiological, operative and histological details were retrieved. The median follow-up was 5 years.

Phyllodes tumors has specific clinical characteristic that can be considered as one of the differential diagnosis of breast lump. All Phyllodes tumors have the potential for recurrence, so surgical treatment with free surgical margin is recommended.

PROGRESS: Completed on 26 Aug, 2015.

PROJECT TITLE: The Characteristics of the Learning Curve for Total Mesorectal Excision for Rectal Cancer
RAC#: 2121018

PRINCIPAL INVESTIGATOR: *Mahfoudh Mohammed*
CO-PRINCIPAL INVESTIGATOR: *Nasser Al Sanea, Alaa Abduljabbar, Samar Al Homoud, Luai Ashari, Ahmad Al Zahrani*

PROJECT DESCRIPTION: A retrospective review of all patients at King Faisal Specialist Hospital & Research Centre Riyadh who underwent total mesorectal excision for rectal cancer between 2000 and 2011. Demographics, tumour characteristics, post-operative complications, local recurrence and the survival rate were retrieved. Multivariate analysis were performed with the following variables: age, gender, cancer staging, type of surgery, tumour location, and number of retrieved lymph node, neo-adjuvant therapy, adjuvant therapy, and operative time, length of hospital stay, follow up duration and removal of other organs.

The incidence of rectal cancer increases with age but local recurrence after rectal cancer excision is not influenced by age 9 and a male has worse prognosis after rectal cancer diagnosis than a female. Advanced stage of rectal cancer has a high incidence of local recurrence rate and an abdominoperineal resection has worse outcome after rectal surgery than anterior resection, it seems worse cases are selected for an abdominoperineal resection, in fact, low rectal cancer has a major role in this. Extraction of twelve or more lymph node after rectal excision improves the tumour staging and this decreases contamination of the staging process. Pre-operative chemoradiation has significantly reduced the local recurrence rate after rectal cancer excision and Post- operative chemotherapy has significantly improved the survival rate after rectal cancer excision. A male gender with narrow pelvis and advanced tumour stage increase the operative time, difficulty of rectal cancer surgery and total length of hospital stay. After rectal surgery 90% of local recurrence is diagnosed within the first 3 years. Large tumour size, low rectal tumour and narrow pelvis are associated with urinary dysfunctions and anastomotic leak. Morbidity after total mesorectal excision is affected by other factors like co-morbidity as assessed by the American Society of anaesthesiology scale. However; morbidity is increased due to wound infection and malnutrition.

PROGRESS: Completed on 24 Jun, 2015.

PROJECT TITLE: Prognostic Value of Pathologic Complete Response after Neoadjuvant Therapy in Rectal Cancer
RAC#: 2121069

PRINCIPAL INVESTIGATOR: *Mahfoudh Mohammed, Alaa Abduljabbar*
CO-PRINCIPAL INVESTIGATOR: *Nasser Al Sanea, Samar Al Homoud, Luai Ashari*

AIM: Evaluate the oncological outcome of patients with a complete pathological response after neoadjuvant chemoradiotherapy for rectal cancer followed by curative rectal surgery.

BACKGROUND: Following neoadjuvant chemoradio-therapy for rectal cancer and curative rectal surgery, 10–25 % of patients are found to have a complete pathological response.

METHOD & POPULATION: A retrospective review of all patients at King Faisal Specialist Hospital & Research Centre Riyadh who underwent preoperative radiotherapy with or without chemotherapy for locally advanced rectal cancer followed by rectal surgery was conducted between 2000 and 2011. Demographics, tumor characteristics, detail of treatment, recurrence and the survival status were retrieved.

Eligibility criteria included: locally advanced rectal cancer with no evidence of metastases at the time of diagnosis, evidence of complete pathological response after preoperative radiotherapy with or without chemotherapy.

RESULTS: Of 345 patients underwent curative rectal cancer surgery after neoadjuvant radiotherapy with or without chemotherapy, the rate of complete pathological response was 7.8 % (n= 27). 20 Patients (74%) had anterior resection and 7 patients (26%) had abdominoperineal resection.

Mean radiation dose was 50 Gy. After mean follow-up 60 months, the 5-year disease-free survival (DFS) was 96 % and overall survival (OS) was 100 %. Distant metastases occurred in 1 patient (4 %).

CONCLUSIONS: Rectal cancer patients achieving complete pathological response after preoperative neoadjuvant chemoradiotherapy for rectal cancer followed by curative rectal surgery had excellent long-term outcomes.

PROGRESS: Completed on 29 Jun, 2015.

PROJECT TITLE: Risk Factors for Anastomotic Leakage After Anterior Resection for Rectal Cancer
RAC#: 2131105

PRINCIPAL INVESTIGATOR: *Osama Almosallam, Nasser Al Sanea*
CO-PRINCIPAL INVESTIGATOR: *Alaa Abduljabbar, Luai Ashari, Mahfoudh Mohammed*

PROJECT DESCRIPTION: Anastomotic leakage remains a major complication after curative resection for rectal cancer. The aim of this study was to identify risk factors for anastomotic leakage.

A retrospective review of the Colorectal Database at King Faisal Specialist Hospital & Research Center-Riyadh (KFSH&RC) was conducted for the period 2001-2011. Demographic data along with patient comorbidities, histopathologic characteristics of the tumors, functional outcome, local recurrence, distant metastasis and survival were extracted from the paper and electronic records. A $p<0.05$ is considered significant. Multivariate and univariate analyses were utilized to assess the significance of each factor studied.

We conclude that The rate of anastomotic leakage was higher among patients who received neoadjuvant chemoradiation.

PROGRESS: Completed on 29 Jun, 2015

PROJECT TITLE: Stenting for Colonic Obstruction: A single Centre Experience
RAC#: 2121119

PRINCIPAL INVESTIGATOR: *Samar Al Homoud*
CO-INVESTIGATOR: *Muhammad Alshammari, LuaiAshari, Nasser Al Sanea, Alaa Abdul Jabbar, Shehri Dafer*

PURPOSE: The introduction of self-expandable metallic stent in the management of acute colonic obstruction as an alternative option to surgery is gaining popularity in providing better quality of life especially for patients with advance cancer as well as a abridge for surgery without the need of stoma creation.

AIM: is to review all patients who underwent insertion of self-expandable metallic colonic stent in a tertiary referring Centre.

METHODS: Prospective review of all patients who underwent colonic stent insertion between

2003-April 2015 including morbidity and mortality using colorectal database.

RESULTS: A total of 103 patients underwent colonic Stenting with a technical success rate of 89 % (13 patients were excluded due to failed stenting), 46 were female and 57 males. Median age was 57 years & follow up of 6 months. Majority of obstruction were due to colorectal cancer (74%) and in the sigmoid colon (69%). 6 cases were done as bridge to surgery. 50% were done by colorectal surgeons using endoscopy and 46% done by interventional radiologists. Four were done combined and all under fluoroscopy guidance.

Procedure related complications were as follow: migration occurred in 13 (13%) patients, re-obstruction in (16%) & perforation rate of 4%.

Only Eleven patients needed stoma creation (11%). Procedures related Mortality was 2% due to perforation & aspiration.

CONCLUSIONS: Expandable stents can provide safe and effective relief of colonic obstruction with shorter hospital stay and should be consider when possible as an alternative to surgery especially in palliative cases.

Our center is one of few centers (if not the only one) in our region that reach to this number with such results as well can perform producer separately at endoscopy or radiology unit.

PROGRESS: Completed on 11 Aug, 2015.

PROJECT TITLE: Accuracy of Pre-operative Radiological Assessment with Histopathological Correlations Suspected Acute Appendicitis: A Retrospective Study
RAC#: 2151149

PRINCIPAL INVESTIGATOR: *Anwar, Ihab*
CO-PRINCIPAL INVESTIGATOR: *Dr. Mariam Ahmed Elsayed*

PROJECT DESCRIPTION: A retrospective chart analysis conducted at the Surgery Department at King Faisal Specialist Hospital and Research Center, Al-Riyadh, KSA. The charts of all adult patients (age 14-99) with suspected acute appendicitis between 1 January 2010 and 30 May 2015 to be reviewed. Patients divided into 3 groups of different imaging routines to assess which one work the best.

The aim of this study is to compare the accuracy of CT and US as diagnostic modalities in suspected cases of acute appendicitis and to set a diagnostic routine to be followed in those cases.

PROGRESS: In progress, preparing for the final report submission.

PROJECT TITLE: Pathological Response After Neoadjuvant Chemotherapy in Invasive Lobular Carcinoma
RAC#: 2151141

PRINCIPAL INVESTIGATOR: *Qahtani, Saad*
CO-PRINCIPAL INVESTIGATOR: *Osama Al Malik, Adher AlSayed*

PROJECT DESCRIPTION: We intended to study the need and benefit of giving neo-adjuvant chemotherapy in Invasive Lobular Carcinoma ILC. Identify a subgroup that may benefit from the neoadjuvant chemotherapy NACT and whether Lobular cancer has a different behavior which warrants a different approach in management.

A retrospective case control study will include all cases with ILC from 2002 to 2012 treated at King Faisal Specialist Hospital & Research Center (KFSH&RC) compared to a matched control group with IDC who received NACT.

The primary aim is to study our experience of Pathological Complete Response (PCR) in ILC treated with NACT. Secondary aims include comparisons with a control group of the more common ductal cancer with regards to PCR, disease free and overall survival.

PROGRESS: Ongoing.

PROJECT TITLE: Pulmonary Metastatectomy: A Report from a Tertiary Care Center (A retrospective Study)
RAC#: 2151047

PRINCIPAL INVESTIGATOR: *Saleh, Waled*
CO-PRINCIPAL INVESTIGATOR: *Ashour, Mohmoud, Al Kattan, Khaled, Hussein Mohamed, Al Shammari Abdullah*

PROJECT DESCRIPTION: A retrospective analysis for all patients who underwent pulmonary metastatectomy at KFSH&RC between January 2000 and January 2014. Will be performed. The charts the patient will be revised certain surgery outcomes will be recorded. The aim of this study is to study the impact of the following factors on disease free survival as well as 5 yeas survival: tumor histology, disease free interval, number of metastases, size of metastases and completeness of resection.

PROGRESS: Ongoing.

PROJECT TITLE: Intra-operative Insertion of Paravertebral Catheter for Continuous Post Thoracotomy Analgesia: A Retrospective Study
RAC#: 2151043

PRINCIPAL INVESTIGATOR: *Ashour, Mohmoud, Al Amassi, Mohamad*
CO-PRINCIPAL INVESTIGATOR: *Al Kattan, Khaled. Saleh, Waled. Abdul Rafy, Mohamed.Hussein, Mohamed, Al Robaidi Hassan, Tulba, Yassir*

PROJECT DESCRIPTION: This study is to review all thoracotomy done in KFSH&RC in the last four years to study the efficacy of the modalities of post- operative analgesia we used, also to compare the complication and side effect of each and to show our experience of intra-operative insertion of paravertebral catheter during thoracotomy and how far it is accessible and effective procedure and to introduce our new technique of inserting it in sub facial space in case of total pluerectomy.

PROGRESS: Ongoing.

PROJECT TITLE: Clinicopathological Features and Outcome of Breast Angiosarcoma: A Study of Sixteen years' Experience in Single Institution. (A Retrospective Study)
RAC#: 2151136

PRINCIPAL INVESTIGATOR: *Badria aljohani, Osama almalik*
CO-PRINCIPAL INVESTIGATOR: *Taher altwajeri, Ihab anwar, Turki alzaydi, Saad alawaad*

PROJECT DESCRIPTION: Breast angiosarcoma is uncommon malignant endothelial vascular neoplasm presented as a solid tumor and palpable mass. Around 20% of angiosarcomas are primary sarcomas.

Angiosarcomas accounts for only 0.04% of all sarcomas, but is frequent in females of age 20-50 years. The natural history of breast angiosarcoma is partially understood. There is a lack of uniformity in the treatment of angiosarcoma. Etiology of breast angiosarcoma is unknown that recur locally and spread widely. Extensive surgery is the only chance of curative treatment for angiosarcoma.

The present study is a retrospective evaluation of patients diagnosed with breast angiosarcomas and admitted to KFSH and RC (2000-2015). All patients had undergone the surgery. The primary objective

of the study was to determine the surgical practice for patients with breast angiosarcoma.

All information such as demographic, clinical and treatment characteristics, follow-up and outcome will be recorded from the charts of patients in the hospital and analyzed statistically.

Finally, we will report our sixteen years of clinical experience for breast angiosarcoma patients admitted to our institution.

PROGRESS: In progress, preparing for the final report submission.

PROJECT TITLE: Relation of Kneeling, Prostration and Sitting on Intra-abdominal Pressure
RAC#: 2151049

PRINCIPAL INVESTIGATOR: *Hussain al khudar, Alaa abduljabar*
CO-PRINCIPAL INVESTIGATOR: *Nasser Al Sanea, Samar Al Homoud, Laui Ashari, Denise Hibbert*

PROJECT DESCRIPTION: To assess the impact of the positions assumed during Muslims prayer on the intraabdominal pressure (IAB) in order to give a postoperative recommendation which may decrease the occurrence of prastomal hernia and stromal prolapse.

Up till now, nothing has been written in the literature about the effect of the prayer of Muslims on the intraabdominal pressure measurement. An increase in the pressure may predispose to parastomal hernia and stromal prolapse development.

This is a prospective cohort study, patients will be enrolled from those admitted under the section of Colon and Rectal surgery at KFSH&RC who had a foly's catheter inserted as part of their post-operative care by the treating team.

PROGRESS: Ongoing.

PROJECT TITLE: The Success Rate of Using Cutting Seton in the Management of Complex Perianal Fistulae
RAC#: 2151086

PRINCIPAL INVESTIGATOR: *Al Mutari Iman*

PROJECT DESCRIPTION: The medical records of all patients treated by the Section of Colon and Rectal Surgery at King Faisal Specialist Hospital and Research Center with complex perianal fistula,. Charts were reviewed between 2000-2012 for the following: demographic data, comorbidities, type of fistula, previous surgical history, post -operative care, number of tightening, recurrence, preoperative and postoperative incontinence and medication used.

Aim: to measure the success rate after thruse of the cutting seton for the treatment of complex perianal fistulae. Secondary end points include assessment of the recurrence rate and incontinence rate.

PROGRESS: Ongoing.

PROJECT TITLE: Feasibility of Minimally Invasive Sub-xiphoid Mediastinoscopy as an Alternative Approach to Chamberlain Procedure
RAC#: 2151036

PRINCIPAL INVESTIGATOR: *Mohd, Abdul Rafy*
CO-PRINCIPAL INVESTIGATOR: *Khaled Al Kattan*

PROJECT DESCRIPTION: Anterior mediastinotomy also known as chamberlain procedure is an established procedure for biopsy of anterior mediastinal mass when other procedures such as CT guided biopsy

is inconclusive. Sub xiphoid mediastinoscopy is minimal procedure an alternative approach for biopsy. We will demonstrate feasibility of minimally invasive procedure over traditional open approach, for biopsy of anterior mediastinal mass.

PROGRESS: Ongoing.

PROJECT TITLE: Outcome of Loop Versus Divided Colostomy in the Management of Anorectal Malformations
RAC#: 2141104

PRINCIPAL INVESTIGATOR: *Ali Al asseri, Saud Alshanafey, Osama Almosallam*

PROJECT DESCRIPTION: Anorectal malformations comprise a wide spectrum of disease, which affect boys and girls, and involve the distal anus and rectum as well as urinary and genital tracts. Colostomy is frequently performed as part of stage management in children with anorectal malformations.

A retrospective review of the pediatric surgery database at KFSH&RC conducted 2000-2014, to compare the outcome of loop colostomy with divided colostomy in anorectal malformation.

In conclusion loop colostomy has shorter operative time and relatively less complication compared to the divided colostomy. Our data suggests that loop colostomy may be more favorable to divided colostomy for ARM patients.

PROGRESS: In progress, final report submitted to complete and close the study.

PROJECT TITLE: Impact of Body Mass Index and Tumor Site on the Staging of Rectal Cancer with Endorectal Ultrasound
RAC#: 2131041

PRINCIPAL INVESTIGATOR: *Ali Al Zahrani*
CO-PRINCIPAL INVESTIGATOR: *Alaa abduljabar, Samar Al Homoud, Laui Ashari*

PROJECT DESCRIPTION: A retrospective case control study, The aim of the present study was to evaluate the accuracy of endorectal ultrasound in preoperative staging of rectal cancer and the effect of BMI and tumour distance on its accuracy.

We reviewed the charts of 436 patients whose ERUS was done for them by the Division of Colon and Rectal Surgery at King Faisal Specialist Hospital and Research Centre from 2003 to 2012. Our analysis excluded 213 patients for various reasons. Accuracy and concordance between the ultrasonographic and clinical stages using magnetic resonance image will be determined. The effect of BMI, tumour distance, gender and the operator on the accuracy of endorectal ultrasound staging was evaluated. A student t-test and Chi square test were used for statistical analysis. $P<0.05$ is considered significant.

PROGRESS: In progress, study in data reporting and analysis phase.

PROJECT TITLE: Spontaneous Endobronchial rupture of Hydatid Cyst Risk Factors and Possible Mechanism
RAC#: 2151212

PRINCIPAL INVESTIGATOR: *Mahmoud Ashour*
CO-PRINCIPAL INVESTIGATOR: *Mohammed Ishaq, Mohammad y. Al AMassi, Mohd Abdul Rafy, Mohd Husein, Waleed Saleh, Khaled Kattan*

BACKGROUND: Pulmonary hydatid cysts are recognized to have high rate of rupture when compared to other affected organs. To identify risk factors associated with endobronchial rupture, we

prospectively analyzed 32 patients with hydatid cysts.

METHODS: All patients undergoing thoracotomies for hydatid cysts were included. Demographic data, site, size, and whether cysts were ruptured or intact, were reviewed. Intraoperatively, diameters of bronchial fistulae were measured. Stepwise multiple logistic regression models was used to analyze results.

RESULTS: There were 21 male and 11 female patients with a mean age of 32 + 15 years (range, 9 to 65 years).Seventeen patients (53.1%) presented with rupture (group 1), while 15 had intact cysts (group 2). Significant difference in mean diameter of fistulae between both groups was seen (6.16 mm ± 2 in group1 versus 0.34 mm ± 0.19 in group 2, P value ≤ .0001), that was identified as the only significant risk factor associated with cyst rupture.

CONCLUSION: At the fistula site, the intra-cystic pressure will be un-opposed, thus leading to herniation of the endocyst membrane, disruption of its integrity and rupture. Therefore, we postulate that this scenario in combination with other co-existing factors could be the possible mechanism for cysts rupture in group 1, rather than group 2 patients. A concept that may also explain, the pathogenesis of the high rate of pulmonary hydatid cysts rupture. Accordingly, we consider these cysts, a naturally occurring model for rupture that should be treated surgically as soon as the diagnosis is made in order to avoid its complications.

PROGRESS: Submitted for consideration to publication.

PUBLICATIONS

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ABSTRACTS & PRESENTATIONS

- Koussayer S. Challenges in Vascular Intervention Symposium, Jeddah KSA, 18–19 April 2015 -Moderator.
- Koussayer S. Presenter/Speaker, Department of Surgery Grand Rounds, " Indication of Hyperbaric Oxygen in Surgery" on 08 January 2015.
- Koussayer S. Presenter/Lecturer, Leipzig Dubai, 14–15 May 2015. IN-Pact Clinical Performance in real world patients population.
- Koussayer S. Patient tailored solutions for challenging TEVAR *Presented/Speaker, LIVE 2015, Endovascular Management of Complex Aortic Occlusion Technique to Avoid Surgery, Greece, 21–23 May 2015.
- Koussayer S., "Patient tailored solutions for challenging TEVAR cases" May 14–15, 2105. LINC Dubai.
- Koussayer S., " IN.Pact clinical performances in real world patients population" May 14–15, 2105. LINC Dubai.
- Koussayer S., "Tips & Tricks for Successful TEVAR Outcome" March 12–14, 2015. PAIRS annual scientific meeting.
- Koussayer S., "An Endovascular Solution for Aortoiliac Disease and Leriche Syndrome: The CERAB Technique" March 12–14, 2015. PAIRS annual scientific meeting.
- Koussayer S., "Tips and tricks in TEVAR deployment for successful outcome"March 11–12, 2015. Bahrain international vascular symposium.
- Koussayer S., "Advanced Aorto-iliac occlusive disease "March 11–12, 2015. Bahrain international vascular symposium.

- Koussayer S., "Stem cell therapy: hope or Myth for No-Options CLI patients? "March 11–12, 2015. Bahrain international vascular symposium.
- Koussayer S., "Endovascular repair of Aorto-iliac occlusion" 18–19 April. 2015. 13th Vascular surgery conference at Saudi German hospital, Jeddah, KSA.
- Koussayer S., "Steps for successful EVAR deployment". 18–19 April, 2015. 13th Vascular surgery conference at Saudi German hospital, Jeddah, KSA.
- Koussayer S., "Indications of HBO in Surgery". January 8, 2015. Presenting at surgery grand round.
- Dr. Waleed Saleh. International Conference "Cystic Fibrosis LungTransplantation in Saudi Arabia", Speaker/Presenter, Cystic Fibrosis Conference and Cystic Fibrosis Awareness Day, 3–5 November 2015.
- Prof. Khaled Alkattan. Lung Cancer Work-up and Staging in Lung Cancer, Master Class, Dubai 15–16 May 2015 - Speaker/Lecturer.
- Prof. Khaled Alkattan. 23rd European Conference On General Thoracic Surgery, Lisbon Portugal 31 May 2015 – 03 June 2015 – Presenter.
- Co Presenter–Prof. Sobhi. Abstract/Conference - AIK overexpression is associated with activation of PI3K/ AKT signaling pathway in PTC, Conference: American Association of Cancer Research, Annual Meeting 2015, At Philadelphia, PA, USA.

15TH ANNUAL SURGICAL RESEARCH & RESIDENTS' DAY, 26 NOVEMBER 2015, KFSH&RC

- Accuracy of Radiological Imaging in the Staging of Rectal Cancer after Neoadjuvant Chemoradiation. Ohoud Alamoudi, Alaa Aduljabbar, Samar Alhomoud, Luai Ashari, Hanaa Alhomoud, Nasser Alsanea.
- Impact of Body Mass Index and Tumor Site on the Staging of Rectal Cancer with Endorectal Ultrasound. Ali Alzahrani, Nasser alsanea, Alaa Abduljabbar, Samar Alhomoud, Luai Ashari.
- The Accuracy of Pre-Operative Radiological Assessment with Histopathological Correlation in Suspected Acute Appendicitis. Ihab Anwar, Mariam Ahmed Elsayed.
- Spontaneous Endobronchial Rupture of Hydatid Cysts: Risk Factors and Possible Mechanism. M. Ashour, M Amassi, M. Ishaq.
- The Never-Ending Dilemma with Lung Cancer; It Never Gives Up! Akram Nurhussen, Lucman A. Anwer, Ayesha N. Anwer, Muhammad Hussein, Khaled M. AlKattan.
- Wandering Spleen: Case Report and Literature Review. Mohammed Almarghoub, Rana Alhossaini, Ihab Anwar. Isolated Idiopathic Common Iliac Artery Aneurysm with Acute Abdomen Presentation in A 9 Year Old Child.M. Tariq Siddique, Alomran Abdullah, M.Anees Sharif, S.Koussayer.
- Phyllodes Breast Tumors: KFSH&RC Experience. Yousef Alalawi, Taher Twegieri, Osama Al Malik, Ihab Anwar, Asma Tulbah
- Can Volar Plate Heal to the Tendon Sheath? Walaa Al Dhubaibban, Mohammad Al Qattan, Abdulaziz Al Abdulkarim.

RELATED ACTIVITIES

We have the following Training Programs in the Department of Surgery:

TWO (2) RESIDENCY TRAINING PROGRAMS

- General Surgery Residency Training Program
  - 23 Residents (KFSH&RC)
  - 13 Rotating Residents
- Plastic Surgery Residency Training Program
  - 2 Residents (KFSH&RC)
  - 4 Rotating Residents

FOUR (4) FELLOWSHIP TRAINING PROGRAMS

- Breast & Endocrine Surgery
- Colorectal Surgery
- Pediatric Surgery
- Thoracic Surgery
- General & Oncology surgery

GENERAL SURGERY RESIDENCY TRAINING PROGRAM

- Weekly Animal Lab Activity, "Training of Surgical Residents in Bowel Anastomosis"
  Every Mondays, 09:00 – 15:00, KFSH&RC
- Weekly Animal Lab Activity, "Microsurgery Training"
  Every Sundays, KFSH&RC
- Surgical Club meeting. 22 February 2015. Four Seasons Hotel, Riyadh.

SYMPOSIA & WORKSHOPS 2015

- 3rd Surgical Basic Review Course
  25–26 February 2015, KFSH&RC
- 2nd Joint Conference of the Saudi-International Colorectal Diseases Forum
  29 March to 2 April, 2015. Four Seasons Hotel, Riyadh
- Animal Workshop on Tracheal and Esophageal Surgeries, ACUC
  10 January 2015 & 20 March 2015, KFSH&RC
- 15th Annual Surgical Research & Residents' Day
  26 November 2015, KFSH&RC

UPCOMING ACTIVITIES 2016

- 4th Surgical Basic Review Course
  26 February 2016, KFSH&RC
- 3rd Saudi-International Colorectal Diseases Forum
  27 to 31 March 2016. Four Seasons Hotel, Riyadh
- Animal Workshop – Video Assisted Thoracic Surgery Lobectomy
  February 20, 2016, KFSH&RC
- 16th Annual Surgical Research & Residents' Day
  03 November 2016, KFSH&RC
- 1st Oncoplastic course, 7–6 February 2016, KFSH&RC
- Surgical Club meeting. 22 February 2015. Four Seasons Hotel, Riyadh

UROLOGY DEPARTMENT

UROLOGY DEPARTMENT

CHAIRMAN
Waleed Al Taweel, MD

THE DEPARTMENT OF UROLOGY CONTINUOUSLY CONDUCTED various research projects specifically in the field of Urology, Andrology/ Infertility and Oncology. On-going research activities primarily focus on treatment for renal stones (initial experience in KFSH&RC with Siemen's Lithotripter), treatment for vesicoureteral reflux, urinary incontinence, bladder augmentation and reconstruction, managing peritoneal carcinomatosis from gynecologic malignancies, bladder/renal cancer management, augmentation cystoplasty (management of urinary bladder dysfunction), Micro TESE, urethral stricture disease (results of hypospadias in adults), infertility/erectile dysfunction and effects of alpha adrenergic blockers on the ureter.

One (1) of the research project was presented during the 30th Annual European Association of Urology Congress 2015 in Madrid, Spain last 20–24 March 2015.

The principal and co-investigators are both actively involved in all the on-going studies in order to come up with the gold standard surgical modality among other available medical/surgical options. They aim to complete research projects which are not only beneficial to the Department or the Hospital but to the society in the long run.

RESEARCH ACTIVITIES

PROJECT TITLE: Extracorporeal Shock-Wave Lithotripsy for Renal Stones: Our Initial Experience with Siemens Lithotripter at KFSH&RC - Riyadh
RAC#215 1123

PRINCIPAL INVESTIGATOR: *Salaheddin Ghiblawi, MD*
CO-INVESTIGATORS: *Noor Junejo, MD*

PROJECT DESCRIPTION: In 1980's, extracorporeal shock wave lithotripsy has become the standard convenient, noninvasive, day case and well established procedure for treatment of renal and proximal ureteric calculi. After the introduction of the original electrohydraulic Dornier HM-3 and its high power delivery, lithotripters have been developed with new sources for generating shock waves, such as electromagnetic and piezoelectric sources. ESWL focusing and imaging devices have been modified over the years to improve the precise delivery of shock waves to the stone. Despite a decreased power delivery that often implies multiple sessions, second and third-generation machines do not require the use of anesthesia, thus achieving greater patient comfort and tolerance. Retrospectively we will evaluate the efficacy and outcomes of Siemens lithoskop. The quick brown fox jumped

PROJECT TITLE: Preoperative Optimization of Testosterone and FSH can Improve Sperm Retrieval Rate by Microsurgical Testicular Sperm Extraction in Patients with Non-Obstructive Azoospermia
RAC#215 1066

PRINCIPAL INVESTIGATOR: *Naif Al Hathal, MD*
CO-INVESTIGATORS: *Noor Junejo, MD, Shahbaz Mehmood, MD*

PROJECT DESCRIPTION: The prevalence of infertility in the society is 15%. Non-Obstructive Azoospermia (NOA) affects approximately 1% of the male population and 10% of men who seek fertility evaluation. Men with NOA have impaired production of sperms in their testes due to various reasons. Although they have overall testicular failure but rare foci of sperm production exist in almost 60% of these patients. These men require some sort of sperm retrieval procedure in combination with intracytoplasmic sperm injection to father a child. There are various method of sperms retrieval with varying degree of safety and efficacy.

Microsurgical testicular sperm extraction (Micro TESE) has become popular procedure in men with non-obstructive azoospermia in terms of safety, efficacy and sperm retrieval rate. It was first described by Schlegel in patients with NOA. Micro-TESE procedure allows surgeon to selectively identify seminiferous tubules most likely to contain spermatozoa having larger and more opaque appearance of those tubules. With micro- TESE, successful sperm retrieval has been reported in men up to 63%, whereas conventional and more limited sperm retrieval procedures have reported success rates from 20% (percutaneous testicular biopsies) to 45% (open testis biopsies. Tsujimura A. et al. Compared sperms retrieval rate (SRR) through Micro TESE with conventional TESE for each pattern of testicular histology in patients with non-obstructive azoospermia and found that microsurgical technique is safer and effective in terms of sperm retrieval rate (SRR) in variety of patients with NOA especially in heterogeneous testicular tubules. Okada et al. In 2002, also found a comparable result with Tsujimura in micro TESE and conventional TESE. In spite of advances in sperm retrieval techniques, there are almost 40-50% of patients with NOA have no sperms to be retrieved with Micro TESE. Most of NOA patients have low testosterone level and it is observed that normal testosterone

level especially intratesticular testosterone is very essential in regulating spermatogenesis in testes. There are still controversies whether preoperative optimizations of spermatogenesis regulating hormone like testosterone and FSH improve sperm retrieval rate in patients with non-obstructive azoospermia. Bobjer J et al. in 2012 found that almost 47% of the patients with NOA have hypogonadism. Preoperative hormone therapy in patients with hypogonadism and NOA has been suggested to improve sperm retrieval rate by Micro TESE in various studies. The rationale of using preoperative hormone therapy is based on the fact that these NOA patients have reduced volume testes which produces less testosterone and result in hypogonadism. Adequate level of intra testicular testosterone is very essential in maintaining spermatogenesis which is compromised in NOA patients. Recently Ashraf et al. in 2014 found that sperm retrieval rate was better in patient with preoperative hormone therapy 53.1% as compare to patients without preoperative hormone therapy 35.6% in patients with NOA. Hussain et al found in his study that preoperative treatment of NOA patients with clomiphene, HCG or hMG improves FSH and total testosterone which result in successful retrieval of sperms (57%) as compare to control group 36.3%. Reifsnyder et al in 2012 found an opposing result of preoperative hormone therapy as compare to above mentioned studies. They observed that preoperative hormone therapy did not improve sperm retrieval rate, clinical pregnancy and live birth rate. They further described that preoperative hormone therapy optimize testosterone level in hypogonadism patients but there was no effect in sperm retrieval rate. So, on the basis of these controversies based on retrospective studies, we want to take the lead of conducting a novel RCT on the outcome of Micro TESE sperm retrieval rate with or without preoperative optimization of testosterone and FSH with hormone therapy in patients with NOA.

PROJECT TITLE: Outcome of Salvage Ureteroneocystostomy in Patient with Failed Dextranomer/ Hyaluronic Acid Copolmer (Dx/Ha) Therapy for Vesicoureteral Reflux
RAC#215 1002

PRINCIPAL INVESTIGATOR: *Ahmad Al Shammari, MD*
CO-INVESTIGATORS: *Shahbaz Mehmood, MD, Mohammed Elshatoury, MD, Yahia Al Sagar, MD*

PROJECT DESCRIPTION: Vesicoureteral Reflux (VUR) is the most common urological entity affecting 1-3% of child in pediatric age group. It results in potentially dangerous morbidities like recurrent urinary tract infection, renal scarring and hypertension leading to end stage renal disease if left untreated. Regarding management of VUR, it always remains the most controversial topic among pediatric urologist. Treatment options range from observation with on or off antibiotics to open surgical correction. In 1986, 'O Donnell and Puri reported endoscopic management of VUR by injecting polytetrafluoroethylene. Various substances were used endoscopically but deflux, a combination of dextranomer and hyaluronic acid first introduced by Sternberg and Lackgren in 1995 proved to be successful in terms of biodegradability, less immunogenic properties and less potential for malignant transformation and efficacy and safety profile.

DX/HA injection therapy became popular among pediatric urologist since its invention as early outcome was successful in patients with VUR. DX/HA has since proved to be a safe and reliable endoscopic alternative to open surgery for treatment of reflux. It has been used in high grade vesicoureteric reflux. Most of the studies on deflux showed a short term elimination of VUR but

few studies showed very disappointing results of deflux on long term follow up especially in patient with high grade VUR. When first injection therapy was failed, many urologists consider the second injection therapy and even the third injection was tried if the second injection failed to resolve reflux. Only a single meta analysis showed the short term outcome of deflux therapy with varying grade of VUR. This study demonstrated a primary success rate of 78.5% for grade 1 and II and 72% for grade III, 63% for grade IV and 51% for grade V reflux.

In the endoscopic era, ureteral reimplantation was considered as salvage procedure when persistent VUR, breakthrough UTI and ongoing renal scarring noted after one or several endoscopic treatment failure. As a matter of fact, salvage ureteroneocystostomy is technically difficult and is not free of operative complication because fibrosis due to previous endoscopic injection therapy. Sencan A et al recently found that previous endoscopic injection although causing some difficulty in dissection but it does not alter the success rate of open ureteroneocystostomy. Louka B et al demonstrated his 7 years experience on outcome of deflux injection therapy in VUR patients. They found that endoscopic injection of deflux remains less effective than surgery in high grade reflux but it is a simple and successful therapy to eliminate reflux in great majority of patients with low grade VUR. Similarly Moreira-Pinto J el al in 2013 found that salvage ureteric reimplantation is not free of complications and technically difficult after failed endoscopic injection therapy but it is feasible and successful option in deflux failure patients.

In conclusion from above mentioned studies that salvage ureteric reimplantation is technically difficult and is not free of morbidities like increased perioperative blood loss, lengthy operative time, difficult dissection, risk of injury to surrounding structure, long hospital stay and more postoperative analgesic requirement. Up till now, no study has been done to compare the outcome of salvage ureteroneocystostomy after failure of endoscopic injection with *de novo* ureteric reimplantation in high grade reflux patients. Furthermore, there may be a shift of paradigm to alter the indication of endoscopic DX/HA therapy in low grade reflux patients and *de novo* ureteroneocystostomy in high grade reflux patients.

PROJECT TITLE: Prevalence of Urinary Incontinence with Sexual Dysfunction in King Faisal Specialist Hospital and Research Centre, Saudi Arabia
RAC#215 1053

PRINCIPAL INVESTIGATOR: *Waleed Al Taweel, MD*
CO-INVESTIGATORS: *Najwa Al Farra*

PROJECT DESCRIPTION: The study will conduct a survey using a self-reporting validated Arabic version of the Urinary Distress Inventory UDI-6 and female sexual index questionnaires (FSFI). Furthermore, the survey will be randomly distributed by two (2) Arabic speaking female therapists, who will distribute and collated the survey and information sheet to the participants while waiting for their appointments visit and follow up with them in case of any queries. The physical therapist assigned to the participants will be tasked with collecting the data sheets from the participants and if they have any queries, they will ask the physical therapist assigned to collect the data sheets.

The study will provide insight in the extend of UI with FSD among the married Saudi female. Furthermore, the knowledge that will be derived from the data will assist in improving treatment and prevention in UI with FSD by the healthcare providers.

PROJECT TITLE: Outcome of Sacral Neuromodulation in Patients with Idiopathic Non-Obstructive Urinary Retention: KSH&RC Experience
RAC#215 1091

PRINCIPAL INVESTIGATOR: *Waleed Al Taweel, MD*
CO-INVESTIGATORS: *Shahbaz Mehmood, MD*

PROJECT DESCRIPTION: Lower Urinary Trach Dysfuntion (LUTD) is highly prevalent and affects the lives of millions of people worldwide. In may manifest as urinary urgency, frequency, incontinence and retention, and/or bowel disorders. The refractory over active bladder (OAB) represents one of challenging dilemma in urological practice. According to definition of International Continent Society, Over Active Bladder symptom complex is urgency with or without urge urinary incontinence, usually with urinary frequency and nocturia. One subclass of the patients present with non-obstructive urinary retention constitutes one of the most difficult class for the urologist to treat. These patients are divided into two (2) categories on the basis of electromyography of external urethral sphincter. Patients who present with burst and complex repetitive discharge on EMG are known to be Idiopathic non-obstructive urinary retention. These symptoms can be distressing and socially disruptive to patients causing significant impairment to their health-related quality of life.

Treatment in the form of urethral dilatation, intermittent catheterization, botulinum toxin injection of the urethral sphincter and alpha-blockers have been tried for women with urinary retention. Spontaneous recovery has not been described and most of these treatments proved unsuccessful. Sacral neuromodulation (SNM), a minimally invasive therapy have been shown to be permissive and effective therapy in restoration of spontaneous voiding and remained effective several years in these urinary retention patients.

PROJECT TITLE: Routine Ureteric Stenting before Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy in Managing Peritoneal Carcinomatosis from Gynecologic Malignancies: A Single-Center Experience
RAC#215 1113

PRINCIPAL INVESTIGATOR: *Ismail Badawi, MD*
CO-INVESTIGATORS: *Ahmed Abu-Zaid, Hussam Abou Al-Shaar, Ayman Azzam, MD, Osma Al-Omar, Mohammed Al Otaibi, MD, Tarek Amin, MD*

PROJECT DESCRIPTION: Iatrogenic ureteric injuries are serious operative adverse events and associated with significant morbidities. While meticulous surgical exploration and subsequent visualization of ureters is ideal in such procedures to avoid ureteric injuries, it is not always possible. The use of prophylactic ureteric stents to prevent ureteric injuries in debulking gynecologic procedures remains controversial. We retrospectively (2010-2014) reported our single-center experience (feasibility and morbidity) with prophylactic ureteric stents as a routine procedure before every cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) in management of patients with primary advanced or recurrent peritoneal carcinomatosis (PC) from various gynecologic malignancies (n=53).

PROJECT TITLE: Bladder Augmentation and Reconstruction Workshop
RAC#215 2004

PRINCIPAL INVESTIGATOR: *Waleed Al Taweel, MD, Abdallah Al Assiri, DVM*

PROJECT DESCRIPTION: The Department of Urology at King Faisal Specialist Hospital is performing numerous augmentation cystoplasties per year in addition to other reconstructive procedures both in the pediatric and adult patients with urinary incontinence. The Hospital has in addition an up-to-date experimental animal facility that hosts annually several surgical training courses in various disciplines. As a training facility, rotating residents in the Department of Urology become exposed to urinary reconstruction procedures in the clinical setting. We designed this 2-day workshop to prepare residents and fellows to become familiar with the surgical techniques involved and the theoretical background. We offer one day experimental animal hands on surgery followed by a second day live surgery transmission performed by skilled urologists. The live transmission will involve explanation and discussion on the clinical background and surgical techniques. As part of their training program, international recognition adds valued to this workshop and helps attract more delegates both at home and from the international prospective urologists interested in reconstruction. We aspire that with the ICS recognition, this workshop will become one of the most important learning opportunities in the Middle East open to delegates worldwide. Residents and fellows will have both theoretical and experimental animal hands on experience for urinary reconstruction before embarking on actual surgery in their prospective training programs. Further, they will have the chance to see live surgery and discuss with expert urologists both the clinical background and surgical techniques.

PROJECT TITLE: Outcome of Bladder Cancer Management
RAC#214 1071

PRINCIPAL INVESTIGATOR: *Mohammed Al Otaibi, MD*
CO-INVESTIGATORS: *Alaa Moukhtar Hammad, MD, Emad Rajih, MD, Mohamed Alawi, MD*

PROJECT DESCRIPTION: To report the outcome of Bladder Cancer management in KFSH&RC between 1995 to present. The pre-operative, intra-operative and post-operative data will be recorded. The parameters will be evaluated where patients' demographics, including the age, gender and time of referral will be obtained. Tumor parameters include the stage, grade, size, numbers and histological subtypes. Management includes endoscopic treatment, intravesical treatment, radical cystectomy, radiotherapy, chemotherapy and palliative management. Outcome measures include, recurrences, disease specific survival, long term survival and surgical outcome.

PROJECT TITLE: Outcome of Augmentation Cystoplasty in the Management of Urinary Bladder Dysfunction
RAC#214 1089

PRINCIPAL INVESTIGATOR: *Waleed Al Taweel, MD*
CO-INVESTIGATORS: *Raouf Seyam, MD, Shahbaz Mehmood, MD, Mohammed Alawi, MD*

PROJECT DESCRIPTION: Augmentation cystoplasty has traditionally been used in the management of short capacity, poorly compliant or refractory overactive bladder. For the last two decades, a rise of new effective treatment modalities like anticholinergic medication, intravesical botulinum toxin and sacral neuromodulation for dertrusor overactivity has reduced the number of augmentation cystoplasty all over the world. A few but significant number of patients refractory to above conservative treatment require surgical intervention with a therapeutic goal to provide urinary storage with low end filling intravesical pressure while preserving upper renal tract, continence, preventing infection and easy voluntary and complete emptying. Augmentation cystoplasty is carried out using open laparoscopic and robotic surgery. A variety of intestinal segments may be used to although

ileocystoplasty is the commonly performed procedure.

Bladder augmentation with gastrointestinal segments is associated with several potential complications such as metabolic disturbances, urinary tract infection, stone formation, incontinence, need for intermittent self catheterization, perforation and risk of malignancy. Augmentation cystoplasty is however, still the gold standard surgical modality among other available surgical options. In this study the principal and co-investigators are set out to review the results of augmentation ileocystoplasty cases performed in KFSH&RC from 2004 to present.

PROJECT TITLE: Micro-Dissection Testicular Sperm Extraction (TESE): Largest Saudi Experience at KFSH&RC
RAC#214 1091

PRINCIPAL INVESTIGATOR: *Naif Al Hathal, MD*
CO-INVESTIGATORS: *Noor Junejo, MD, Hamad Alakrash, MD, Abdullah Alfakhri, MD*

PROJECT DESCRIPTION: Non-obstructive azoospermia (NOA) testicular failure affects approximately 1% of the male population and 10% of men who seek fertility evaluation. Azoospermic men with testicular failure (non-obstructive azoospermia) have either Sertoli cell-only pattern, maturation arrest, or hypospermatogenesis on testis biopsy. Until recently, it was assumed that men with non-obstructive azoospermia were untreatable. Sperm retrieval (SR) coupled with intracytoplasmic sperm injection (ICSI/IVF) is the only hope for men with NOA who seek conception.

Conventional testicular biopsy and testicular sperm extraction have sperm retrieval rate (SRR) of 20-45% in men with NOA, however, micro dissection testicular sperm extraction (Micro-TESE) has yielded a higher sperm retrieval rate worldwide up to 80%. Micro-TESE is now considered the gold standard of sperm retrieval in NOA. Despite this increased success, the ability to counsel patients pre-operatively on their probability of successful sperm retrieval has remained challenging. A combination of variables such as age, serum FSH and inhibin B levels, testicular size, genetic analysis, history of Klinefelter syndrome, history of cryptorchidism or varicocele and histopathology on diagnostic biopsy may provide valuable prognostic tools regarding successful sperm retrieval in men with NOA.

In the Hospital, 131 cases for Micro-TESE were done from 2 Jul 2011 to 22 Dec 2013. This work is considered descriptive retrospective chart review study based on the physician's experience on relatively recent modification of technique for sperm retrieval. The primary end point is sperm retrieval rates for Micro-TESE at King Faisal Specialist Hospital and Research Centre. Secondary end points are correlation of testicular histopathology to SRR, pregnancy rates, take home babies with previous negative conventional testicular biopsy and complications.

PROJECT TITLE: Surgical Outcome of Urethral Stricture Disease" "Results of Hypospadias in Adults
RAC#213 1102

PRINCIPAL INVESTIGATOR: *Waleed Al Taweel, MD*
CO-INVESTIGATORS: *Alaa Mokhtar Hammad, MD, Noor Junejo, MD, Emad Rajih, MD*

PROJECT DESCRIPTION: To review the urethral stricture disease with intervention that includes:

- Endoscopic treatment with outcome
- Urethroplasty outcome

All cases were reviewed and outcome data were documented.

Endoscopic treatments showed success with initial trial by visual internal urethrotomy only.

Perineal Urethroplasty showed success rate more than around 90% and to be the standard care after initial failure of endoscopic treatment in certain circumstances.

PROJECT TITLE: The Effect of Alpha Adrenergic Blockers on the Ureter: As In Vivo Study in the Dog
RAC#205 0032

PRINCIPAL INVESTIGATOR: *Waleed Al Taweel, MD*
CO-INVESTIGATORS: *Alaa Mokhtar Hammad, MD, Raouf Seyam, MD, Raafat El-Sayed, Falah Al-Mohana, Ghanem Ashraf*

PROJECT DESCRIPTION: To elucidate the mechanism by which alpha blockers modify the function of the canine ureter. The result may explain how these medications facilitate expulsion of ureteric stones in clinical practice.

PROJECT TITLE: The Correlates of the Male Sexual Dysfunction in Liver Transplantation Patients and the Impact of Management
RAC#209 1016

PRINCIPAL INVESTIGATOR: *Waleed Al Khudair, MD, Said Kattan, MD, Raouf Seyam, MD*
CO-INVESTIGATORS: *Alaa Mokhtar Hammad, MD, Mohamed Alsebayel, Ahmed El-Sakka*

PROJECT DESCRIPTION: Establish the prevalence of erectile dysfunction in patients receiving liver transplantation. The etiology of erectile dysfunction will be elucidated and managed accordingly. Contributing factors will be identified and preventive measures will be advised.

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مستشفى الملك فيصل التخصصي ومركز الأبحاث
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