



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







*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.*



## MESSAGE FROM THE CHIEF EXECUTIVE OFFICER

As a world class health care facility the King Faisal Specialist Hospital & Research Centre strives to deliver services of the highest quality and achieve optimal outcomes. In order to maintain this level of service in the future the General Organization focuses on continual performance to provide excellence and innovation in healthcare.

Research is an integral component of the approved Vision 2020 Strategic Plan of King Faisal Specialist Hospital and Research Centre (Gen. Org.) and it is often research and development that differentiates the best from the best.

By investing in research, education and innovation the General Organization has been rewarded by international and regional recognition and leadership in many fields, including cancer, genetics, transplantation, radiotherapy, and more.

In 2014 the Research Centre has achieved many significant basic, translational and service activities including:

- Implementation of the most current radiotherapeutic modalities
- Regional leadership in accreditation and education for Radiation Medicine
- Major contributions in disease screening and diagnostics
- Cellular and molecular research in cancer, diabetes and infectious diseases
- High impact publications in the biology of cancer
- Participation in the International Cancer Genome Consortium through investigation of Papillary Thyroid Carcinoma



**Qasim Al Qasabi, MD,**  
**FRCSI, FACS**  
*Chief Executive Officer, KFSH&RC*

- Establishment of an active research program in transplantation medicine
- World leadership in inherited rare diseases research
- Establishment of a Saudi Human Genome Variant database
- Development of state-of-the-art informatics solutions for genotyping and phenotyping and establishing the foundation for personalized medicine

On behalf of the General Organization I commend the achievements of the Research Centre in 2014 and look forward to continued success. Maintaining the General Organization's regional and international prominence as a major healthcare provider is firmly bound to an active and strong research program and I encourage everyone to build on the foundations and tradition of basic and translational research at the King Faisal Specialist Hospital and Research Centre.

## MESSAGE FROM THE EXECUTIVE DIRECTOR OF THE RESEARCH CENTRE

Life science research and biotechnology are strongly associated with the advancement of clinical care. Fields such as stem cell biology, tissue and cellular re-engineering, systems biology, genomics and proteomics have led to remarkable improvements in health. Developments of new drugs, biologicals, vaccines and diagnostics have resulted in significant advances in the prevention, diagnosis and treatment of diseases. Increasingly the effective application of these advances in patient care is dependent on local studies at the population level or indeed in the current era of personalized medicine, at the level of each individual. Much of our research at KFSH&RC is dedicated towards study of regionally important areas impacting health of Saudis and the introduction of the most effective current therapeutic modalities to this population.

During 2014 programs within the Research Centre have expanded our capacity in the areas of stem cell biology and transplantation, engaged in international consortiums profiling cancer, invested heavily in genomic studies and the development of big data management and analytical pipelines. In addition to ongoing research programs in cellular and molecular biology, infectious diseases and environmental studies, significant resources have been invested in establishing epidemiological studies and bio-banking. These initiatives address key disease areas in the Saudi population. Our participation in the Saudi Human Genome Program has led to unprecedented characterization of inherited diseases at a national level and has established KFSHRC as a world leader in this area. Development of a Saudi Human Genome Variant



**Sultan Al-Sedairy, PhD**  
*Executive Director, Research Centre*

database is a major achievement and a central component in positioning our institution to engage in the practice of personalized medicine. The translation of our research activities remains evident in the extensive service work performed, in screening and diagnosis, dedicated to better treatment and prevention of disease. Our research and development has also been central to the provision of cutting edge modalities in radiation medicine for both imaging and treatment.

Key indicators of research including the procurement of external funding and the presentation and publication of our work consistently place KFSHRC as a regional leader performing at better than the world averages. As always whilst our achievements are good they only challenge us to be better. I welcome the research participation of all in the common interests of better patient care and achievement of the strategic goal of KFSHRC, to be a world-leading Institution of excellence and innovation in healthcare.



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**THE RESEARCH CENTRE  
RESEARCH REPORT**



THE  
BIOMEDICAL PHYSICS  
DEPARTMENT



## BIOMEDICAL PHYSICS

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**T**he Biomedical Physics Department is committed to contributing to 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 foster 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 achievements of the Department for the year 2014 are largely associated with the services provided 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.

**Belal Mofteh, PhD, FCCPM**  
CHAIRMAN

**Fernandez, Aileen Jessica, BSc**  
(Trainee: until March 2014)

**San Pedro, Mildred, BSc**  
(RC Grant – Resignation: August 2014)

**Venturina, Nikki, BSc**  
(RC Grant)

**Veridiano, Josephine, BSc**

The summary of achievements of the Biomedical Physics Department during the year 2014 is as follows:

- Vital role in the effective and safe clinical utilization of the five major radiotherapy treatment modalities namely, TomoTherapy, CyberKnife, TrueBeam, Mobetron and Nucletron HDR for cancer patients. In addition, we have commissioned the IntraBeam Intraoperative Radiotherapy system, and started to use it for patient treatment.
- Primary organizer of the International Conference on Radiation Medicine (ICRM2014), held on 16–20 February 2014, in collaboration with the King Abdullah City for Atomic and Renewable Energy (KACARE), Saudi Food and Drug Authority (SFDA), Ministry of Health (MoH), International Atomic Energy Agency (IAEA), World Health Organization (WHO), the Radiological Society of Saudi Arabia (RSSA), the Saudi Society of Medical Radiological Technologists (SSMRT). The event was enriched by 65 international speakers and over 100 national speakers 14 continuing education courses, 35 workshops, as well as exhibiting sponsors whose contributions have come to about 3 million Saudi Riyals, and was attended by more than 2,000 participants, making it one of the biggest international scientific/clinical conferences in the region.
- Hosting of the 5-week Medical Physics and Radiation Protection Training Course for the Ministry of Health from 21 December 2014.
- 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.
- Selection of KFSH&RC to pilot and host the first “IAEA/ARASIA Regional Residency Training Program for Medical Physicists in Radiation Oncology at KFSH&RC”. This program is ongoing and being implemented in close collaboration with various leading health institutions in the Kingdom; King Abdullah City for Atomic and Renewable Energy; and three ARASIA member states. The program is running successfully with 5 residents under the supervision of the Biomedical Physics Department at KFSH&RC.
- Co-Authoring of one of the prestigious IAEA Training Course Series peer-reviewed publications: TRS#56, Postgraduate Medical Physics Academic Programs, Vienna, 2013, which is endorsed by the International Organization for Medical Physics (IOMP).
- Leading of efforts for re-accreditation of our radiation physics procedures, radiotherapy machines output and the American RTOG protocols by the Radiological Physics Center 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.
- Establishment of a residency program in Nuclear Medicine Physics which is supported by the IAEA. The application has been submitted to the IAEA with the support of the King Abdullah City for Atomic and Renewable Energy (KACARE) this year. It has received a preliminary approval by IAEA and KA CARE.
- Successful completion of and compilation of final reports for two KACST projects.
- Two of our KACST Biotechnology grant proposals were scored highly (13/15) by the American Association for the Advancement (AAAS) in USA, the publisher of the premier global Science weekly.
- Submission of final report to KACST for research project entitled “Functional MRI of infants & toddlers with autism.
- 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).

- Acceptance and Presentation of three abstracts on Radiation Oncology at the prestigious European Society for Radiotherapy and Oncology (ESTRO) meeting in Vienna, Austria.
- 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 Canadian College of Physicists in Medicine (CCPM), 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.
- One of our senior medical physicists participated in the American Association of Medical Dosimetrists (AAMD) 2014 Radiation Oncology Resources Plan Challenge, and his submitted plan was ranked number 10 among 1800 submitted plans worldwide.
- Key role in several other major projects, including the radiological (radiology and radiotherapy) equipment procurement and shielding designs for King Abdullah Center for Oncology and Liver Diseases (KACO&LD).
- While our department is mostly a service-oriented one, our staff managed to publish 11 peer-reviewed manuscripts and are Principal Investigators of 6 approved research projects funded by King Abdulaziz City for Science and Technology (KACST).
- Member of the WHO global biodosimetry laboratories network for radiation emergencies (<http://www.biodosenet.org>).
- Acquiring of new and renewal of KACST/KA CARE licenses to import radioactive materials.
- Biomedical Physics of KFSH&RC-Jeddah is under the supervision of the Biomedical Physics Department, KFSH&RC-Riyadh.
- Acceptance testing, QA, calibration of medical imaging equipment.
- Review and evaluation of radiotherapy and diagnostic equipment for KACC&LD including Linear Accelerators, Portable X-Ray, CT, Angiography, C-Arm, Fluoroscopy, Ultrasound, Mammography, and Radiography X-Ray.
- Preparation of technical specifications for MRI scanners for general use and special applications for the Radiology Equipment Purchasing Committee for KACO&LD and evaluation of the vendors' offers.
- Lectures to the Fellows in the Nuclear Medicine Section and in Diagnostic Imaging Course at Alfaisal University.
- Fourteen lectures given for the Ministry of Health Course for Nuclear Medicine Technologists, Corp. Executive Hotel, Riyadh, 20 – 24 April, 2014.
- Lectures to Nuclear Medicine Fellows titled "Nuclear Medicine Imaging Systems: Gamma Cameras".
- Presentations at Alfaisal University and to MRI technologists at King Saud University.
- Completion of training of two students from Um Al-Qura University, Makkah, one from King Fahad University of Petroleum and Minerals in the department.
- Ongoing work on the research project whose objective to analyze bone metastasis in various cancer types.
- Working on a database for Nuclear Medicine Quality Control to be used to save the data acquired during the daily, weekly, quarterly and annual quality control tests of imaging and ancillary equipment.
- Collaborative work with Department of Radiology on the analysis of the PET images using the GE imaging application PETVCAR.
- Working on the International Atomic Energy Agency book chapter entitled "Devices for Evaluating Imaging Systems in Nuclear Medicine Physics, A Handbook for Teachers and Students".
- Collaboration for on a new project with researchers from the Cyclotron and Radiology departments on F18-Choline imaging of various cancer indications such as prostate and HPC.
- Supervision of two PhD and three MSc students in the department.

- Submission two new proposals for KACST funding in the area of functional imaging.
- News on RC-KFSH Twitter about our publication documenting genetic individual variation in radiosensitivity and reaction to radiotherapy which was highly cited above world and US average.
- Acceptance and presentation of abstracts and posters by staff members in local and international conferences.
- Management of a standard national biodosimetry laboratory in Saudi Arabia to estimate radiation doses received in cases of accidental overexposure.
- Recipient of an appreciation for highly cited manuscript that scored above the world and U.S. average in the field of Radiology and Nuclear Medicine.
- Guest Editor of a Research Topic hosted by Frontiers in Oncology with accepted 10 manuscripts.
- Gamma sterilization for KFSH&RC Bone bank, Cell Biology, Comparative Medicine and supplies of ART laboratory and biomedical research section.
- Renewal of the Gamma Facility ISO certification. Passed the annual auditing required for the ISO re-certification.
- Management of dosimetry laboratory in cooperation with KACST on development of the 3-D Gel compositions. Upgrade of the laser scanner for the 3-D Gel verification system is ongoing for radiation therapy.
- Survey and decontamination of 251 radiation rooms and 251 patients for radiation level.
- KACST QA accreditation for our TLD Laboratory.
- Monitoring for occupational dose for 15,924 radiation workers.
- Leak tests for 519 sealed sources and radiation producing equipment.
- Processing of 16,281 Thermoluminescent dosimetry badges.
- Management and transportation of 108 radioactive wastes.
- Survey of 3,420 outgoing radioactive materials.
- Provision of physics consultation services within and outside KFSH&RC.
- Increase in number of clients following establishment

of a Business Office and appointment of a Business Coordinator to attend to marketing and managing the income producing activities of the department.

- Approval and supervision of one Saudi Career Development Program participant.
- Ongoing efforts of the Biomedical Physics Department with KFSH&RC stakeholders for the establishment Master's Degree Program in Medical Dosimetry. Contract agreement between King Faisal Specialist Hospital and Research Centre and Southern Illinois University has been drafted. This program is a unique opportunity to educate and train dosimetrists at KFSH&RC through SIU in the United States, and an ideal solution to global shortage of qualified medical dosimetrists to hire and responding to the staffing needs for the KACO&LD.

Details of activities and achievements of the following sections/areas of responsibilities for 2014 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-present). (Designated a Model Proposal).

**INVESTIGATORS:** Belal Mofthah (Principal Investigator), Ghazi Alsbeih, Mohammed Mohiuddin, Mohammed Al Shabanah, Manhar Vora, Faisal Al-Rumayan

**PROGRESS:** The project is to establish intraoperative proton therapy technique for the first time. It utilizes the current CS-30 cyclotron and the developed expertise with KFSH&RC.

**PROJECT TITLE:** Development of Novel 3D Gel Dosimetry System for Radiation Oncology Treatment Verification.

A grant proposal approved by the KACST Advanced and Strategic Technologies Program of the National Comprehensive Plan for Science and Technology and reviewed by the American Association for the Advancement of Science (AAAS) in USA.

The project aim was to develop new and improved 3D polymer gel dosimeter for the verification of innovative radiotherapy treatment techniques so that a safe treatment can be delivered to cancer patients. (Approved Budget SR 2,000,000, January 2011-December 2012).

**INVESTIGATORS:** Belal Mofthah (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:** Developing Biological Dosimeters for the Assessment of Radiation Overexposure in Nuclear Accident. KACST Project#-MED749-20. ORA # 2110 005.

**INVESTIGATORS:** Ghazi Alsbeih, Awad Al-Zahrany, Belal Mofthah, Mohamed Shoukri

This project aimed at developing biological dosimeters to help the nation's ability to respond to sporadic and

mass radiation casualty incidents by assisting in the evaluation of radiation overexposure. The project has been completed this year with high AAAS score. The primary aim was to build biological dosimetry capabilities in Saudi Arabia and to construct the dose-response calibration curve for dicentric chromosomes pre-required to estimate doses received. These were accomplished and a fully-fledged biodosimetry laboratory was established, a standard dose-response calibration curve was determined in Saudi Arabia (Figure 1). Networking was established with international biodosimetry network in cooperation with IAEA/WHO.

Being the first in the region, the formation of this expert laboratory in biodosimetry may have an impact on the ability of Saudi Arabia to respond to nuclear events. It enhances the nation's casualty management capabilities by providing a platform for diagnostic technique for triage and medical management purposes as part of a national emergency response plan. In line with NSTIP strategic plan, the project involved knowledge and biotechnology transfer and trained scientists and technical staff in sample preparation for cytogenetic dicentric analysis and other biomarkers currently under development and will be submitted as a new project, further linking and complementing radiation physics to biotechnology.

**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

The Kingdom of Saudi Arabia has recently launched the Atom for Peace initiative to profit from the tremendous capabilities of nuclear sciences while ensuring international confidence in its peaceful applications. This project lends support to these efforts by providing estimate of the range of radiation

sensitivity of Saudi individuals and their susceptibility to radiation injuries that are precursors of cancer development. The identification of genetic loci that confer sensitivity or resistance to ionizing radiation will pave the way to personalized radiation treatment of cancer patients and estimate risk of premeditated or accidental radiation exposure. In this radiogenomic study we hypothesized that single nucleotide polymorphisms (SNPs) can affect radiation sensitivity. To identify SNPs linked to increased radiation risk we follow two approaches, candidate genes involved in radiation response (TP53 codon 72, HDM2 promoter 309, CDKN1A (p21) C31A, ATM G1853A, XRCC1 G399A, XRCC3 C241T, Ku80 (XRCC5) A2790G, DNA Ligase IV C9T, DNA-PKcs A3434G, and TGF-beta T10C) and genome-wide (Whole-Genome 2.6M CytoScan cytogenetics arrays).

We have so far 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 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. An estimated 75% of the objectives have been achieved. A 1-year extension is requested to complete the study.

**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 involvement of HPV infection in Head & Neck, colorectal and breast cancers in Saudi patients is unknown. The aim of this retrospective exploratory study is to determine the distribution of HPV infections and genotypes in these cancers, their pathological association with p16 protein expression and their potential association with host genetic predisposing single nucleotide polymorphic (SNP) variations in TP53 and HDM2 genes. Paraffin-embedded tumor samples from 400 adult Saudi patients treated for Head and Neck (particularly oro-pharynx; n=200), colorectal (n=100) and breast (n=100) cancers will be examined. Genetic predisposing SNPs will be determined by comparison with genotypes frequencies in 400 age/gender matched controls without cancer. Response to cancer treatment will be examined for possible association with HPV status, p16 protein positivity and SNPs genotypes.

In the 1<sup>st</sup> year of this project we have obtained lists of Head & Neck, colorectal and breast cancer patients who were treated at KFSH&RC. So far we have reviewed medical record of 230 patients and had processed 108 for HPV detection (Figure 3). We have also set up the required techniques including real-time PCR for HPV integration. Results showed absence of HPV infection in the 108 oropharyngeal tumors. Testing HPV integration in 81 cervical cancers indicated that about one-third of samples have highly integrated HPV-16 in the host genome.

**PROJECT TITLE: Quantification of Bone Metastasis in Whole-body Images of PET/CT.**

Although the overall incidence of bone metastasis is not known, over one-half of people who die of cancer in the United States each year are thought to have bone involvement. In this study we developed

a method to quantify the metabolic and anatomic changes induced by bone metastases in cancer patients using PET/CT images. The quantitative parameters along with the structural changes seen by CT bone window may serve as a useful tool in assessing the response of bone metastases to therapy.

**INVESTIGATOR: Omer Demirkaya**

**PROGRESS:** Seventy three patients with no prior history of chemo or radiotherapy who had definite bone metastases documented by PET/CT using the PET/CT system and other conventional modalities were selected for the study. PET/CT images were resampled to the same pixel size. Then the bone structure was segmented using a threshold of 150 HU. After the segmentation, the 50% of the maximum SUV within the bone mask was used to identify bone lesions in each slice. Using the ROIs defined at 70% of the max, the lesion characteristics including the mean HUs were computed from the PET/CT images. The lesions were subjected to the visual confirmation by an experienced PETCT physician who also categorized them based on the appearances in the CT bone window as lytic, sclerotic, mixed, or no-change type. The lesion characteristics were compared using statistical methods.

**PROJECT TITLE: A Non-Invasive and Sensitive Molecular Blood Assay to Evaluate Treatment Response / Relapse in Women With Breast Cancer.**

**CO-INVESTIGATOR: Omer Demirkaya**

Our role as a co-investigator in this project (RAC# 2110 20) 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: Omer 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 JCI A surveys.

**PROJECT TITLE:** Oncological applications of F-18 Fluorocholine PET/CT; a prospective study to evaluate its role in patients' management.

**PRINCIPAL INVESTIGATOR:** Belal Moftah

**CO-INVESTIGATOR:** Omer 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. A grant proposal has been submitted to KACST for grant support.

**PROJECT TITLE:** Localizing hypoxic tumor volumes for radiotherapy treatment planning

**CO-INVESTIGATOR:** Omer 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.

## **FUTURE RESEARCH DIRECTION**

Although providing clinical services is our primary responsibility, the Department will continue to participate in more research and development projects. The future research directions for each section of Biomedical Physics are highlighted in the respective sectional reports.

## **PUBLICATIONS**

The publications of the Biomedical Physics Department for the year 2014 are listed in each section's annual report.

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## BUSINESS OFFICE

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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

**Eng. Saad Bin Jamaan**

HEAD

**Ms. Hanan Shetayeh**

(Grant Employee)

### **BPD BUSINESS OFFICE ACTIVITIES**

Customers queries by:

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

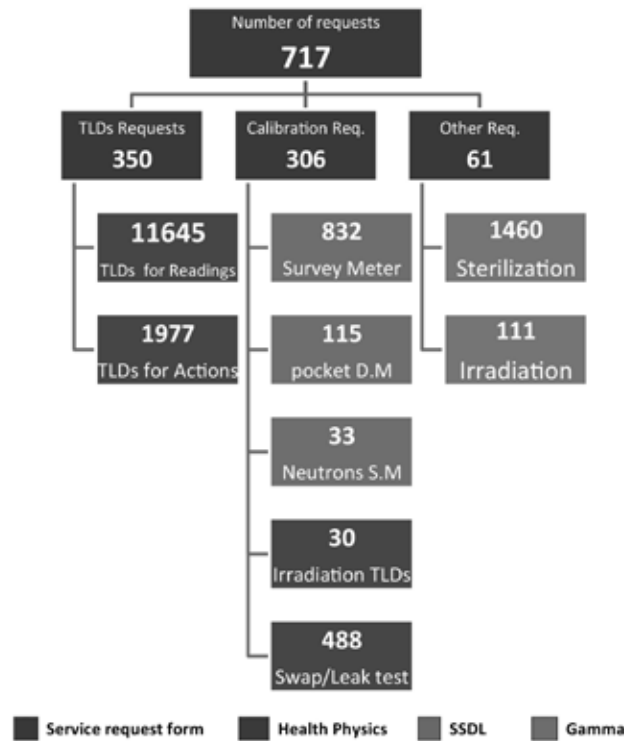
Queries about:

- Biomedical Physics Department Services
- Price quotations
- 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



Received by



Delivered by





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## CLINICAL DOSIMETRY AND TREATMENT PLANNING UNIT

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2014 has continued to follow the 2013 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 2015 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 a 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.

**Christine Higby, MA, CMD**  
HEAD

**Manal Awidh, BSc, CMD**  
(Grant Employee)

**Osama Hassad, BSc, CMD**

**Arwa Helmi, BSc**

**Ghadeer Nazer, BSc, CMD**

**Wedyan Safar, BSc, CMD**

**CORE SERVICE ACTIVITIES**

ACTIVITIES	YEAR 2014
Monitor Unit (MU) Calculation/2-Dimensional Contour	
Total Body Irradiation (TBI) Calculation	
3-Dimensional CT Treatment Planning	1388
Electron Cut-out Measurement	35
Intensity Modulated Radiation Therapy (IMRT)	2
RapidArc	541
Tomotherapy	250
CyberKnife	83 (Jan–Sept)
TLD Dosimetry	
Intraoperative	44
High Dose-Rate (HDR) Brachytherapy	158
Low Dose-Rate (LDR) Brachytherapy	0
Clinical Consultation	
<b>TOTAL PROCEDURES</b>	
<b>PATIENTS</b>	
<b>MANHOURS</b>	

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, Overtime 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.

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## **GAMMA IRRADIATION FACILITY**

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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.

**Akram Al-Moussa, MSc**  
HEAD

**Saad Bin-Jamaan, BSc**  
**Edilberto Delos Reyes**

### **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 ongoing. 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 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.

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## HEALTH PHYSICS SECTION

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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.

**Fareed Mahyoub, MSc, MIPEM**

HEAD

**Celestino S. Lagarde, BSc**

**Noor Al-Edan, BSc**

**(Grant Employee)**

**Ibrahim Al-Gain, MSc**

**Huda Al-Ghamdi, BSc**

**(Grant Employee)**

**Shaima Al-Shora, BSc**

**(Grant Employee)**

### HEALTH PHYSICS ACTIVITIES

The table below 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	5013
No. of Personnel Radiation Monitoring performed	21401
Patients surveyed for radiation level	254
Patients rooms surveyed for radiation level	254
Patients rooms decontaminated	254
Leak test for sealed sources and radiation producing equipment	600
TLD badges irradiated for quality control of TLD readers of outside facilities	5013
Consultative advice provided	5
Training courses & educational lectures provided	5

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## IMAGING PHYSICS SECTION

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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.

**Omer Demirkaya, PhD, DABSNM**  
HEAD

**Ibrahim Al-Anazi, MSc, ABHP, ABMP**  
**Refaat Y. Al-Mazrou, MSc, FIPEM**  
**Adnan Z. Al-Watban, PhD, FIPEM**

## 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 for the new imaging areas in the North Tower and the outpatient x-ray and mammography rooms.

## 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 was significant to the ICRM2014 conference which is probably one of the largest conferences held in the Kingdom with about 2000 attendees. Our section plays a leading role in the Radiology Residents Physics Review (RRPRC) Course given to the Radiology residents. We held the 10<sup>th</sup> RRPRC course this year. Our section staff also contributed to

the training course for the Nuclear Medicine fellows in our institution. Currently, the section staff is also contributing 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 will be conducting a workshop on Gamma Camera Quality Control for the 6<sup>th</sup> Gulf Nuclear Medicine conference to be held 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:** Quantification of Bone Metastasis in Whole-body Images of PET/CT.

**INVESTIGATOR:** Omer Demirkaya

**PROJECT DESCRIPTION:** Although the overall incidence of bone metastasis is not known, over one-half of people who die of cancer in the United States each year are thought to have bone involvement. In this study we developed a method to quantify the metabolic and anatomic changes induced by bone metastases in cancer patients using PET/CT images. The quantitative parameters along with the structural changes seen by CT bone window may serve as a useful tool in assessing the response of bone metastases to therapy.

**PROGRESS:** Seventy three patients with no prior history of chemo or radiotherapy who had definite bone metastases documented by PET/CT using the PET/CT system and other conventional modalities were selected for the study. PET/CT images were resampled to the same pixel size. Then the bone structure was segmented using a threshold of 150 HU. After the segmentation, the 50% of the maximum SUV within the bone mask was used to identify bone lesions in each slice. Using the ROs defined at 70% of the max, the lesion characteristics

including the mean HUs were computed from the PET/CT images. The lesions were subjected to the visual confirmation by an experienced PETCT physician who also categorized them based on the appearances in the CT bone window as lytic, sclerotic, mixed, or no-change type. The lesion characteristics were compared using statistical methods.

**PROJECT TITLE: A Non-invasive and Sensitive Molecular Blood Assay to Evaluate Treatment Response / Relapse in Women With Breast Cancer.**

**CO-INVESTIGATOR: Omer Demirkaya**

Our role as a co-investigator in this project (RAC# 2110 20) 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: Omer 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 JCI/A surveys.

**PROJECT TITLE: Oncological Applications of F-18 Fluorocholine PET/CT; a Prospective Study to Evaluate its Role in Patients' Management.**

**CO-INVESTIGATOR: Omer 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. A grant proposal has been submitted to KACST for grant support.

**PROJECT TITLE: Localizing Hypoxic Tumor Volumes for Radiotherapy Treatment Planning.**

**CO-INVESTIGATOR: Omer 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.

## **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. This research will also assist the institution in optimizing modality utilization (PET/CT versus just CT or MRI) thus minimizing the time of diagnosis and reducing radiation exposure to patients.

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). The Section is in the process of establishing a residency program in Nuclear Medicine Physics. The application has been submitted to the IAEA with the support of the King Abdullah City for Atomic and Renewable Energy (KACARE) and is under review.

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## MOLECULAR AND FUNCTIONAL IMAGING

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Presently in its sixth year of existence, the Molecular and Functional Imaging (MFI) group has pursued both intramural and extramural funding in congruence with its strategic plan. After the resignation of Dr. M. Gary Sayed, Dr. Rafat Mohtasib became the acting head of the section.

**Gary Moussa Sayed, PhD,FACNM**  
HEAD (RESIGNATION: 10 JULY 2014)

**Rafat Mohtasib, PhD**  
ACTING HEAD

Two research grant applications were submitted to KACST this year. One of these grant proposals titled "Health-related quality of life and disability status among multiple sclerosis patients switched to Natalizumab and Fingolimod – MRI Study". The other research grant proposal titled "Assessment & Development of Functional Imaging Protocols In Epilepsy".

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 titled "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 submitted the final report in February 2014 to KACST for our previously approved and funded KACST project titled "Functional MRI of Infants & Toddlers with Autism"

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## RADIATION BIOLOGY SECTION

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The past 2014 was a remarkable year for the discipline of radiation biology and oncology that provides the biological basis of the many uses of radiation in medical and allied health professions. Nationally, our small group of Radiation Biology was successful in having new projects and publications. Internationally, a collaborative multi-center research project has succeeded in publishing a landmarking radiogenomic paper in the influential Nature Genetic journal.

**Ghazi Alsbeih, PhD**

HEAD

**Najla Al-Harbi, BSc**

**Muneera Al-Buhairi, BSc**

**Khaled Al-Hadyan, MSc**  
(on PhD study leave)

**Sarah Bin Judia, BSc**  
(formerly Al-Qahtani)

**Sara El-Ewisy, BSc**  
(Grant Employee)

**Nikki Venturina, BSc**  
(Grant Employee)

**Jenelyn Castro, BSN, RN**  
(Grant Employee)

**Jameelah Almusallam, BSc**  
(Trainee)

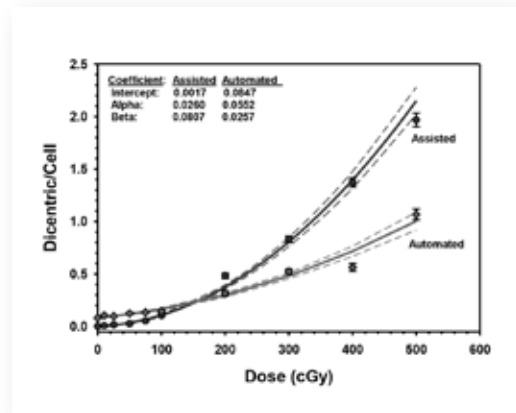
## RESEARCH PROJECTS

**PROJECT TITLE:** Developing Biological Dosimeters for the Assessment of Radiation Overexposure in Nuclear Accident. KACST Project#-MED749-20. ORA # 2110 005.

**INVESTIGATORS:** Ghazi Alsbeih, Awad Al-Zahrany, Belal Mofthah, Mohamed Shoukri

This project aimed at developing biological dosimeters to help the nation's ability to respond to sporadic and mass radiation casualty incidents by assisting in the evaluation of radiation overexposure. The project has been completed this year with high AAAS score. The primary aim was to build biological dosimetry capabilities in Saudi Arabia and to construct the dose-response calibration curve for dicentric chromosomes pre-required to estimate doses received. These were accomplished and a fully-fledged biodosimetry laboratory was established, a standard dose-response calibration curve was determined in Saudi Arabia (Figure 1). Networking was established with international biodosimetry network in cooperation with IAEA/WHO.

Being the first in the region, the formation of this expert laboratory in biodosimetry may have an impact on the ability of Saudi Arabia to respond to nuclear events. It enhances the nation's casualty management capabilities by providing a platform for diagnostic technique for triage and medical management purposes as part of a national emergency response plan. In line with NSTIP strategic plan, the project involved knowledge and biotechnology transfer and trained scientists and technical staff in sample preparation for cytogenetic dicentric analysis and other biomarkers currently under development and will be submitted as a new project, further linking and complementing radiation physics to biotechnology.



**Figure 1.** Linear-quadratic dose-response calibration curves (solid lines) for dicentric chromosomal aberrations induced by 320 keV X-rays in lymphocytes derived from four Saudi volunteers. Data points represent the yield of dicentric per metaphase scored using either manually assisted (circles) or automated (diamonds) mode. Broken lines are the 95% confidence limits calculated assuming Poisson distribution. Error bars represent the standard errors.

The various activities of this reference biodosimetry laboratory can also provide officials with tools to distinguish affected from the worried individuals, and alleviate public concerns about the health effects of possible radiological exposures. It also adds depth to information for decision-makers and public health officials who assess the magnitude of public, medical, occupational and accidental radiation exposures in addition to providing a platform for advanced education, research and development.

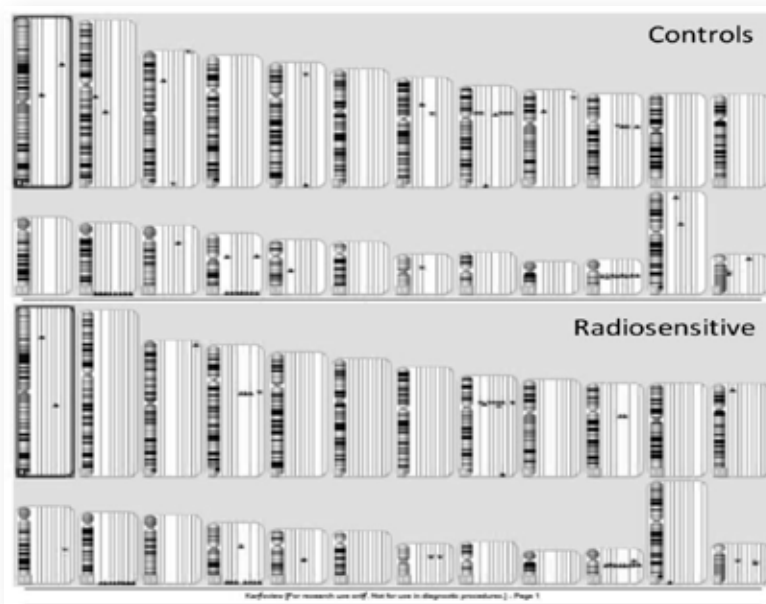
**PROJECT TITLE:** Assessing the Genotypes' Distribution of Genetic Polymorphic Variations and their Impact on the Risk of Radiation Exposure in Saudi Individuals. KACST, National Plan for Science and Technology (# 11-BIO1429-20). ORA/RAC # 2120 003.

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

The Kingdom of Saudi Arabia has recently launched the Atom for Peace initiative to profit from the

tremendous capabilities of nuclear sciences while ensuring international confidence in its peaceful applications. This project lends support to these efforts by providing estimate of the range of radiation sensitivity of Saudi individuals and their susceptibility to radiation injuries that are precursors of cancer development. The identification of genetic loci that confer sensitivity or resistance to ionizing radiation will pave the way to personalized radiation treatment of cancer patients and estimate risk of premeditated or accidental radiation exposure. In this radiogenomic study we hypothesized that single nucleotide polymorphisms (SNPs) can affect radiation sensitivity. To identify SNPs linked to increased radiation risk we follow two approaches, candidate genes involved in radiation response (TP53 codon 72, HDM2 promoter 309, CDKN1A (p21) C31A, ATM G1853A, XRCC1 G399A, XRCC3 C241T, Ku80 (XRCC5) A2790G, DNA Ligase IV C9T, DNA-PKcs A3434G, and TGF-beta T10C) and genome-wide (Whole-Genome 2.6M CytoScan cytogenetics arrays).

We have so far 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 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. An estimated 75% of the objectives have been achieved. A 1-year extension is requested to complete the study.



**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.

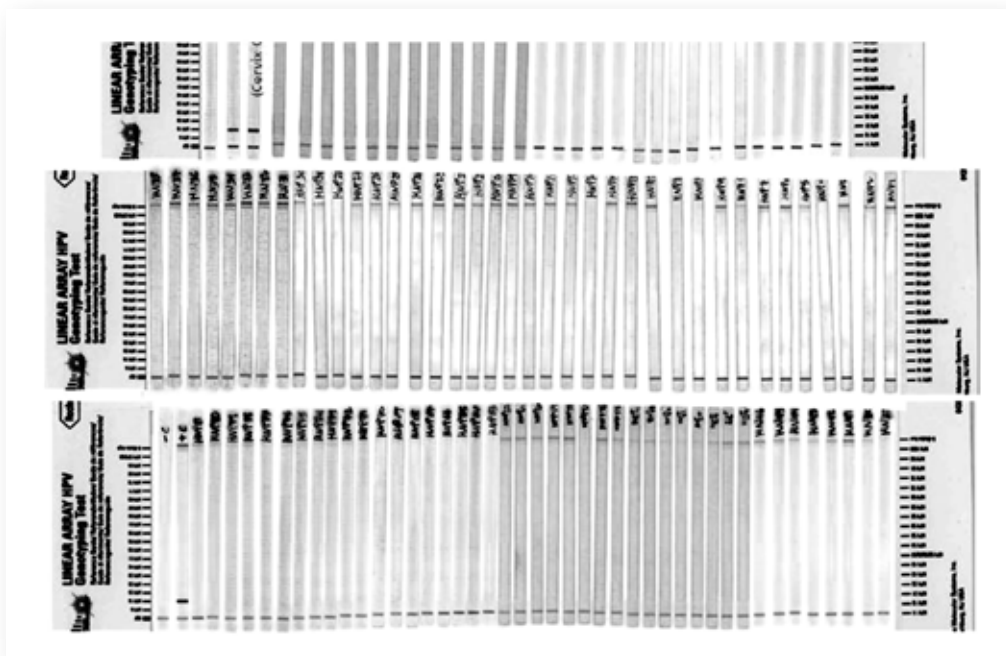
**PROJECT TITLE:** Role of HPV Infection and Genetic Predisposition in Colorectal, Breast and Head and Neck Cancers in Saudi Arabia. National Science Technology and Innovation Plan (NSTIP) (# 12-MED2945-20). ORA/RAC # 2130 025.

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

The involvement of HPV infection in Head & Neck, colorectal and breast cancers in Saudi patients is unknown. The aim of this retrospective exploratory study is to determine the distribution of HPVs infections and genotypes in these cancers, their pathological association with p16 protein expression and their potential association with host genetic predisposing single nucleotide polymorphic (SNP) variations in TP53 and HDM2 genes. Paraffin-embedded tumor samples from 400 adult Saudi patients treated for Head and Neck (particularly oro-pharynx; n=200),

colorectal (n=100) and breast (n=100) cancers will be examined. Genetic predisposing SNPs will be determined by comparison with genotypes frequencies in 400 age/gender matched controls without cancer. Response to cancer treatment will be examined for possible association with HPV status, p16 protein positivity and SNPs genotypes.

In the 1<sup>st</sup> year of this project we have obtained lists of Head & Neck, colorectal and breast cancer patients who were treated at KFSHRC. So far we have reviewed medical record of 230 patients and had processed 108 for HPV detection (Figure 3). We have also set up the required techniques including real-time PCR for HPV integration. Results showed absence of HPV infection in the 108 oropharyngeal tumors. Testing HPV integration in 81 cervical cancers indicated that about one-third of samples have highly integrated HPV-16 in the host genome.



**Figure 3.** HPV results obtained using the Linear Array HPV Genotyping Test (Roche Diagnostics), showing negative (-C) and positive (+C) controls, and a positive pathological sample of cervix carcinoma along with the 108 HPV-negative oropharyngeal cancers.

## Summary of pertinent accomplishments during 2014

CATEGORY	NUMBER	DESCRIPTION
Services	2	Maintain a standard national biodosimetry laboratory in Saudi Arabia to estimate radiation doses received in cases of accidental overexposure. Member of the WHO global biodosimetry laboratories network for radiation emergencies ( <a href="http://www.biodosenet.org">http://www.biodosenet.org</a> ).
Honor	1	Received appreciation for highly cited manuscript that scored above the world and U.S. average in the field of Radiology and Nuclear Medicine.
Publications	6	Published 6 manuscripts in international journals and conference proceedings
Editorial	1	Guest Editor of a Research Topic hosted by Frontiers in Oncology with accepted 10 manuscripts.
Public media	1	Posted news on RC-KFSH Twitter about our publication documenting genetic individual variation in radiosensitivity and reaction to radiotherapy which was highly cited above world and US average.
Posters	6	Having 6 abstracts and posters presentation in conferences.
Students supervision	9	Supervise projects of 1 PhD, 2 MSc, 3 Mawhiba students; and examine 3 radiation oncology residents
Teaching lectures	24	Academic lectures residents and technologists
Seminars	6	5 lectures in international and 1 local instances
Conference organization	1	International Conference on Radiation Medicine (ICRM2014). Member, Local Speaker, Chairman, Coordinator and Instructor. KFSHRC, 17-20 Feb. 2014.

**ACCOMPLISHMENTS DURING 2014****PUBLICATIONS**

Original papers published in peer-reviewed journals:

- Khaled Al-Hadyan, Sara Elewisy, Belal Moftah, Mohamed Shoukri, Awad Alzahrany, Ghazi Alsbeih. Establishing Cytogenetic Biodosimetry Laboratory in Saudi Arabia and Producing National Calibration Curve of Dicentric Chromosomes as Biomarker for Medical Dose Estimation in Response to Radiation Emergencies. *3 Biotech journal*, online 18 April 2014. DOI: 10.1007/s13205-014-0217-x.
- Alsbeih G, Brock W, Story M. Misrepair of DNA double-strand breaks in patient with unidentified

chromosomal fragility syndrome and family history of radiosensitivity. *International Journal of Radiation Biology*. 2014 Jan;90(1):53-9. doi: 10.3109/09553002.2014.859764. PMID: 24164476.

**Review manuscripts:**

- Ala-Eddin Al Moustafa, Rana Al-Awadhi, Nabihha 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.

**Conference proceedings:**

- Tuskasz Król, Ghazi Alsbeih, Christophe Badie, Joanna Polanska. Impact of missing genotype imputation on the power of Genome Wide Association Studies. IWBBIO 2014: International Work-Conference on Bioinformatics and Biomedical Engineering. 7–9 April, 2014. Granada, Spain.
- Joanna Zyla, Christophe Badie, Ghazi Alsbeih, Joanna Polanska, Modelling of genetic interactions in GWAS reveals more complex relations between genotype and phenotype. Bioinformatics 2014: 5<sup>th</sup> International Conference on Bioinformatics Models, Methods and Algorithms, 3–6 March, 2014. ESEO, Amgers, Loire Valley, France.

**Invited articles:**

- Foray N, Badie C, Alsbeih G, Lambin P, Geara F, Taghian AG, Deschavanne P, Gueulette J, Courdi A, Chavaudra N, Fertl B. Edmond-philippe malaise (1930–2013): a lifetime of perseverance leads to the cellular definition of intrinsic radiosensitivity. *Int J Radiat Oncol Biol Phys*. 2014 Apr 1;88(5):1215-7. doi: 10.1016/j.ijrobp.2013.12.049.

**Acknowledged in:**

- McKenzie ND, Kobetz EN, Ganjei-Azar P, Rosa-Cunha I, Potter JE, Morishita A, Lucci JA III, Guettouche T, Hnatyszyn JH and Koru-Sengul T (2014) HPV in HIV-infected women: implications for primary prevention. *Front. Oncol.* 4:179. doi: 10.3389/fonc.2014.00179.

**Others:**

- Guest Editor of a Research Topic titled: HPV Associated Cancers, Socio-Economic Disparity and Vaccination, hosted by Frontiers in Oncology, speciality section: Cancer Epidemiology and Prevention journal. My role is to define the research topic, write up an introduction, select

associate editors, invite potential contributors, find and assign reviewers, assess the review process and take final decision. This is a complex creative research work that requires a deal of scientific, administrative and organizational skills. The topic Editors are:

- Ghazi A. Alsbeih, King Faisal Specialist Hospital & Research Centre, Saudi Arabia
- Silvia De Sanjose, Catalan Institute of Oncology, Spain
- Ala-Eddin Al Moustafa, McGill and Concordia Universities, Canada
- The topic has received 18 confirmed intents for contribution and have accepted 10 manuscripts. Description of the research topic and manuscripts accepted can be found at the link ([http://www.frontiersin.org/Cancer\\_Epidemiology\\_and\\_Prevention/researchtopics/HPV\\_Associated\\_Cancers\\_Socio-E/1337](http://www.frontiersin.org/Cancer_Epidemiology_and_Prevention/researchtopics/HPV_Associated_Cancers_Socio-E/1337)).

**ABSTRACTS, POSTER PRESENTATIONS & DISCUSSIONS**

- Ghazi Alsbeih, Rafa Al-Meer, Najla Al-Harbi, Muneera Al-Buhairi, Sara Al-Qahtani, Nikki Venturina, Salma Majid, Faisal Abou Tarboush. Genetic biomarkers of radiation sensitivity: association with SNPs and molecular cytogenetic CNVs. Submitted to 15<sup>th</sup> International Congress on Radiation Research (ICRR 2015). 25–29 May 2015. Kyoto, Japan.
- S Aldelaijan, S Devic, M Shehadeh, F Alzorkany, F Alrumayyan, K Al-Hadyan, G Alsbeih, J Seuntjens, B Mofteh. Dose Calibration and Monitoring for Radiobiological Experiments with Low Energy Proton Beams. Poster. ESTRO Forum, 24–28 April 2015. Barcelona. Spain.
- Alsbeih G, El-Sebaie M, Al-Harbi N, Al-Qahtani S, Al-Buhairi M, Venturina N, Alrajhi N, Tulbah A. HPV infection and its association with genetic predisposition in cervical and other related cancers in Saudi Arabia: Implication for prevention and vaccination. Poster. UAE Cancer Congress, 30 October – 1 November 2014. Dubai, UAE
- Ghazi Alsbeih, Rafa Al-Meer, Najla Al-Harbi, Muneera Al-Buhairi, Sara Al-Qahtani, Nikki

- Venturina, Khaled Al-Hadyan, Salma Majid, Mohamed Shoukri, Faisal Abou Tarboush. Association between Genetic Polymorphic Variations and Radiation Sensitivity Phenotype in Saudi Individuals. Poster. Human Genome Meeting 2014, Genome Variation and Human Health. 27-30 April, Geneva, Switzerland.
- Fareed Mahyoub, Khaled Al-Hadyan, Saad Binjamaan, Celestino Lagarde, Heba Al-Humidan, Arwa Helmi, Sara Elewisy, Omar Noor, Huda Mosallay, Gary Sayed, Ghazi Alsbeih and Belal Mofrah. Radiation Monitoring of Radiation Workers in Saudi Arabia. Service Review 2006–2012. Poster. International Conference on Radiation Medicine “ICRM 2014”, at InterContinental hotel, Riyadh, Saudi Arabia, 16–20 February 2014.
  - Rafa Al-Meer, Najla Al-Harbi, Muneera Al-Buhairi, Sara Al-Qahtani, Nikki Venturina, Salma Majid, Mohamed Shoukri, Faisal Abou Tarboush, Ghazi Alsbeih. Assessing the Genotypes’ Distribution of Genetic Polymorphic Variations and their Impact on the Risk of Radiation Exposure in Saudi Individuals. Poster. ICRM 2014: International Conference on Radiation Medicine. February 17–20, 2014. Riyadh, Saudi Arabia.

#### **NEWS OF SCIENTIFIC ACTIVITIES, RELEASE TO MEDIA AND PUBLIC FORUMS**

- Posted news on Twitter about our publication documenting genetic individual variation in radiosensitivity and reaction to radiotherapy which was highly cited above world and US average. ([https://twitter.com/RC\\_KFSHRiyadh/status/542721438344425472](https://twitter.com/RC_KFSHRiyadh/status/542721438344425472)).

#### **STUDENTS AND TRAINEES’ SUPERVISION**

- External Examiner, Radiobiology final oral exam, R1 Residency Program (3 residents), Radiation Oncology Department, King Fahad Medical City, Riyadh, 12 June 2014.

#### **POSTGRADUATE STUDENTS’ THESIS SUPERVISION:**

- PhD Student: Rafah Al-Meer. In collaboration with the Faculty of Sciences, King Saud University. January 2011–5 June 2014.
- MSc Student: Aisha Al-Qarni. In collaboration with the Faculty of Sciences, King Saud University. September 2014–August 2015.
- MSc Student: Wejdan Al-Qahtani. In collaboration with the Faculty of Sciences, King Saud University. September 2014–August 2015.

#### **UNDERGRADUATE STUDENTS’ PROJECTS SUPERVISION**

- Role of HPV in cancer development. Ibn Sina (Mawhiba) summer program. 3 high school students: Alwagd Almassri, Bushra Alfaihi, Hanin Bashikh. KFSHRC, Riyadh, 8–26 June 2014.

#### **TEACHING COURSES AND ACADEMIC LECTURES**

##### **24 lectures as follows:**

- Radiobiology for Ministry of Health radiological technologists: 3 academic lectures (1. Basic radiation Biology, 2. Health Effects of Ionizing Radiation, 3. Clinical Radiobiology) as part of the recurrent 5-weeks Medical Physics and Radiation Protection Training Course. KFSH&RC, RC Room 304, 14 December 2014–15 January 2015.
- Radiobiology for Radiologists: 3 academic lectures and 1 Raphex mock examination as part of the 10<sup>th</sup> Annual Radiological Physics Review Course, KFSH&RC, a 2-weeks intensive course (14–26 June 2014) for residents in radiology in preparation for board certification. Radiology Dept. 25 June 2014.
- Radiobiology for Residents in Nuclear Medicine: 6 academic lectures as part of the Radiology Department Activity – half academic day, KFSH&RC, Radiology Conference Room, 9 and 12 June 2014.

- Radiobiology for Graduate Radiology Technologists: 6 academic lectures (1. Human Cell Biology, 2. Fundamental Principles of Radiobiology, 3. Molecular and Cellular Radiobiology, 4. Response of Organ System to Radiation Exposure, 5. Deterministic Effects of Radiation Exposure, 6. Stochastic Effects of Radiation Exposure) as part of the curriculum to obtain MSc in Radiological Sciences. Alfaisal University, Riyadh, 2 and 8 April 2014.
- Radiobiology for Resident in Radiology: 3 academic lectures as part of the Department Activity – half academic day lectures, KFSH&RC, Radiology Conference Room, 11 February 2014.
- Introduction to Radiation Biology “What you need to know”. 2 academic lectures for 2<sup>nd</sup> year Medical students. Alfaisal University, Riyadh, 30 January 2014.

#### SEMINARS, LECTURES AND EDUCATIONAL ACTIVITIES

##### International:

- **Lecture:** Cytogenetic biodosimetry to estimate radiation doses received in accidental radiological exposures. International Conference on Radiation Biology (ICRB 2014), Frontiers in Radiobiology: Immunomodulation, Countermeasures & Therapeutics. 11–13 November 2014. New Delhi. India.
- **Lecture:** National Biodosimetry Laboratory in Saudi Arabia. In Radiation Protection & Radiobiology, 19 February 2014. ICRM 2014. February 17–20, 2014. Riyadh, Saudi Arabia.
- **Lecture:** Radiation Biology. In Introduction to Radiation Medicine, 18 February 2014. ICRM 2014. February 17–20, 2014. Riyadh, Saudi Arabia.
- **Lecture:** Variation of Radiosensitivity between Individuals. In Radiation Protection & Radiobiology, 18 February 2014. ICRM 2014. February 17–20, 2014. Riyadh, Saudi Arabia.
- **Lecture:** Tutorial on Radiation Biology. In World of Medical Physics, 16 February 2014. ICRM 2014. February 17–20, 2014. Riyadh, Saudi Arabia.

##### Local:

**Oral Presentation:** Ghazi Alsbeih, Khaled Al-Hadyan, Sara Elwisy, Nikki Venturina, Medhat El-Sebaie, Mohamed Shoukri, Belal Moftah. Establishing Biological Dosimetry Laboratory for the Assessment of Radiation Overexposure in Cases of Radiological Accidents in Saudi Arabia. ICRM 2014. February 17–20, 2014. Riyadh, Saudi Arabia.

#### ORGANIZATION OF CONFERENCES, SYMPOSIUMS AND WORKSHOPS

\* International Conference on Radiation Medicine (ICRM2014). Member of the Organizing Committee, Local Speaker, Chairman of the Radiobiology & Radiation Protection Track and Sub-Committee, Coordinator of related lectures and organizer and Instructor of the Radiobiology and Radiation Protection Workshop titled: Biological Dosimetry. KFSHRC, 17–20 Feb. 2014.

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## RADIATION ONCOLOGY PHYSICS

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Our Radiation Oncology Physics team played a vital role in the effective and safe clinical utilization of the five major radiotherapy treatment modalities namely, TomoTherapy, CyberKnife, TrueBeam, Mobetron and Nucletron HDR. In addition, we have commissioned the IntraBeam Intraoperative Radiotherapy system, and have started to use it for patient treatment. We have obtained accreditation of our radiation physics procedures, machine output and the American RTOG protocols by the Radiological Physics Center of M.D. Anderson Cancer Center.

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. Abdullah Al-Kafi, passed the American Board of Radiology board certification exams in 2014. One of the section members, Mr. Ahmad Nobah, participated in the AAMD 2014 Plan Challenge, and his submitted plan was ranked number 10 among 1800 submitted plans.

During this reporting year, the Section was the primary organizer of the International Conference on Radiation Medicine (ICRM2014), held on 16-20 February 2014. The event was enriched by 65 international speakers and over 100 national speakers as well as exhibiting sponsors whose contributions have come to about 3 million Saudi Riyals, and was attended by more than 2,000 participants.

The Radiation Oncology Physics staff participated in writing the equipment specifications for KACO&LD. They evaluated the shielding design for the radiotherapy vaults, and the tenders submitted for equipment procurement for KACO&LD. Our staff members were also involved in the training of 5 International Atomic Energy Agency (IAEA) residents.

A major retention and recruitment drive has been initiated by the Section Head to offer competitive packages to our qualified staff, and future recruits.

**Belal Mofteh, PhD, FCCPM**  
HEAD

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

## RESEARCH PROJECTS

**PROJECT TITLE:** Development of Novel 3D Gel Dosimetry System for Radiation Oncology Treatment Verification.

**PROJECT DESCRIPTION:** The project is to establish gel dosimetry as a verification tool for radiotherapy treatments. The project aim is to develop new and improved 3D polymer gel dosimeter for 3D radiotherapy treatment planning and verification of complicated radiotherapy treatment techniques so that a safe treatment can be delivered to cancer patients.

**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:** Intra-Operative Proton Radiotherapy (IOpRT).

**PROGRESS:** A grant proposal was submitted to KACST's Advanced and Strategic Technologies program of the National Comprehensive Plan for Science and Technology. Proposal was approved with high score by the AAAS Review Panel. It was concluded in August 2014 (KACST Grant Project # #11-BIO1428-20. Approved funding: SR 2.0 million).

**PROGRESS:** Final report for the project has been compiled and submitted to KACST Advanced and Strategic Technologies in August 2014. Publications are ongoing.

## FUTURE CLINICAL RESEARCH DIRECTION

**PROJECT TITLE:** Localizing hypoxic tumor volumes for radiotherapy treatment planning.

**PROJECT DESCRIPTION:** The project's aim is to produce O-15 tracers, which can be used for phantom and animal studies as a hypoxia marker for identifying

tumor sub-volumes lacking oxygen in cancer patients. The identified hypoxic volumes will be used for biological dose optimization and dose escalation protocols to be further investigated through controlled clinical trials.

**PROGRESS:** Grant proposal written and will be submitted in the next KACST submission cycle February 2015. Multi-disciplinary research group have been formed from different KFSH&RC departments as well as from two international institutions, McGill and Vrije Universiteit Amsterdam.

## PUBLICATIONS

### Publications in refereed journals

- A. Nobah, S. Aldelaijan, S. Devic, N. Tomic, J. Seuntjens, M. Al-Shabanah, B. Moftah, "Radiochromic film based dosimetry of image-guidance procedures on different radiotherapy modalities," accepted for publication for the *Journal of Applied Clinical Medical Physics* Vol 15, 2014
- N. Tomic, C. Quintero, B. R. Whiting, S. Aldelaijan, H. Bekerat, L. Liang, F. DeBlois, J. Seuntjens, and S. Devic. "Characterization of calibration curves and energy dependence GafChromic™ XR-QA2 model based radiochromic film dosimetry system," *Med. Phys.* 41 (6) 062105 (2014)
- Ahmad Nobah, Mohammed Mohiuddin, Slobodan Devic, Belal Moftah, "Effective spatially fractionated GRID radiation treatment planning for a passive grid block", *British Journal of Radiology* (BJR), Br J Radiol 2015;88:20140363
- Khaled Al-Hadyan, Sara Elewisy, Belal Moftah, Mohamed Shoukri, Awad Alzahrany, Ghazi Alsbeih, Establishing cytogenetic biodosimetry laboratory in Saudi Arabia and producing preliminary calibration curve of dicentric chromosomes as biomarker for medical dose estimation in response to radiation emergencies, *3 Biotech Springer Open* (April 2014), DOI 10.1007/s13205-014-0217-x, <http://www.springer.com/home?SGWID=0-0->

1003-0-0&aqId=2651209&download=1&ckval=c8f1b37d3c38c7f5dc8e57761a4186f0

### Submitted publications

- Ghada Aldosary, Ahmad Nobah, Faisal Al-Zorkani, Slobodan Devic and Belal Mofteh, "A practical method of modeling a treatment couch using cone-beam CT for IMRT and RapidArc treatment delivery", Accepted by *Medical Dosimetry* (2014).
- M Abdullah Al Kafi, Umar M Mwidu, Belal Mofteh, Evaluation of a Novel 3D Water Scanner for Cyberknife Measurement, submitted to *Journal of Applied Clinical Medical Physics* (2014).

### Posters at conferences and meetings

- G. Aldosary, A. Nobah, F. Al-Zorkani, Slobodan Devic and Belal Mofteh, Influence of a Modeled Treatment Couch on Dose Distributions During IMRT & RapidArc Treatment Delivery, Abstract, Poster Session 1, Annual Scientific Meeting of the Canadian Organization of Medical Physicists (COMP), Banff, Alberta, Canada, 9–12 June, 2014.
- S. Aldelaijan, A. Nobah, S. Devic, N. Tomic, J. Seuntjens, B. Mofteh, Dosimetric assessment of state of the art image guidance procedures using radiochromic films, Poster abstract E33-0324, ESTRO 33, Vienna, Austria, April 4–8, 2014.
- Nobah, M. Mohiuddin, S. Devic, B. Mofteh, Treatment planning using passive grid block for spatially fractionated GRID radiation therapy, E-poster abstract E33-0186, ESTRO 33, Vienna, Austria, April 4–8, 2014.
- T. Amin, A. Azzam, R. Mahmood, Z. Hassan, H. Alselham, M. Hussain, B. Mofteh, Clinical Implementation of IntraOperative Electron Radiation Therapy (IOeRT) at KFSH&RC, Poster Session 19A: Radiation Oncology Track, Poster abstract 14, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- S. Devic, S. Aldelaijan, F. Alrumayan, M. Shehadeh, F. Alzorkani, J. Seuntjens, A. Almousa, B. Mofteh, Assessment of Radiochromic Film for Dosimetry of Low Energy Protons, Poster Session 19B: Medical Physics Track, Poster abstract 36, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- U. Mwidu, R. Mahmood, M. Hegazy, Z. Hassan, B. Mofteh, M. Neimatallah, Image Adapted High Dose Rate Brachytherapy (HDR) at KFSH&RC Based on GEC-ESTRO Guidelines, Poster Session 19B: Medical Physics Track, Poster abstract 38, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- F. Alzorkani, S. Aldelaijan, F. Alrumayan, M. Shehadeh, S. Devic, M. Alfatih, N. Maalej, B. Mofteh, Comparison Between Proton Beam Characteristics of a Radiopharmaceutical Cyclotron Using Havar and Kapton as a Beamline Window, Poster Session 19B: Medical Physics Track, Poster abstract 39, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- Naga, N. Hussain, B. Mofteh, Commissioning Experience of a Cone-Beam Computed Tomography System and Implementation of Image-Guided Radiation Therapy Technique, Poster Session 19B: Medical Physics Track, Poster abstract 44, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- M. Hussain, Z. El Taher, H. Alselham, B. Mofteh, Commissioning of Mobetron for Intra-operative Radiation Therapy, Poster Session 19B: Medical Physics Track, Poster abstract 45, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- M. Al Kafi, A. AlMousa, K. Rabaeh, A. Basfar, B. Mofteh, Patient Specific Quality Assurance Using 3D Polymer Gel, Poster Session 19A: Radiation Oncology Track, Poster abstract 47, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- F. Mahyoub, K. Al-Hadyan, S. Binjamaan, C. Lagarde, H. Al-Humidan, A., S. Elewisy, O. Noor, H. Mosallay, G. Sayed, G. Alsbeih, B. Mofteh, Radiation Monitoring of Radiation Workers in

Saudi Arabia. Service Review 2006–2012, Poster Session 19D: Radiation Biology and Safety Track, Poster abstract 97, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.

#### Presentations at conferences and meetings

- B. Mofteh, F. Alrumayyan, S. Aldelaijan, M. Shehadeh, F. Alzorkani, M. Alshabanah, J. Seuntjens, S. Devic, Dosimetric characterization of low energy protons for intra-operative radiation therapy, ESTRO 33, Vienna, Austria, April 4–8, 2014.
- S. Aldelaijan, A. Nobah, S. Devic, N. Tomic, J. Seuntjens, M. Al Shabanah, B. Mofteh, Radiochromic Film Dosimetry of Image Guidance Systems in Radiotherapy, Oral abstract, ROP Abstract 1, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- R. Mahmood, A. AlSuhaibani, M. ElSebaie, N. AlSanea, B. Mofteh, M. Mohiuddin, PET and MR Based Selective Dose Escalation With Simultaneous Integrated Boost (SIB) Using Image Guided Intensity Modulated Radiotherapy in Rectum Cancer, Oral abstract, RO Abstract 4, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- M. Hegazy, R. Mahmood, I. Al-Badawi, H. Al-Husaini, C. Higby, B. Mofteh, Bone Marrow Sparing Image Guided Intensity Modulated Radiotherapy with Simultaneous Integrated Boost (SIB) in Locally Advanced Cervix Cancer, Oral abstract, RO Abstract 5, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- B. Mofteh, F. Alrumayyan, S. Aldelaijan, M. Shehadeh, F. al-Zorkany, J. Seuntjens, M. AlShabanah, S. Devic, Feasibility Testing Intra-Operative Radiation Therapy Using Low Energy Protons, Oral abstract, ROP Abstract 6, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- B. Mofteh, F. Mahyoub, I. Algain, M. Ezzat, T. Salim, M. Ahmed, Assessment of Occupational Radiation Dose in KFSH&RC from 2005 to 2012, Oral abstract, RBS Abstract 8, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- A. Almousa, K. Rabaeh, A. Basfar, A. Al Kafi, B. Mofteh, Characterization of Two Newly Developed Polymer Gels for Radiotherapy Verification, Oral abstract, ROP Abstract 9, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- G. Alsbeih, K. Al-Hadyan, S. Elwisy, N. Venturina, M. El-Sebaie, M. Shoukri, B. Mofteh, Establishing Biological Dosimetry Laboratory for the Assessment of Radiation Overexposure in Cases of Radiological Accidents in Saudi Arabia, Oral abstract, RBS Abstract 9, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- C. Higby, B. Mofteh, R. Mahmood, A. Nobah, G. Nazer, O. Hassad, Volumetric Arc Therapy (VMAT) is Superior to 3D Conformal Radiotherapy (CRT) for Locally Advanced Cervix Cancer - A Dosimetric Comparison, Oral abstract, RO Abstract 11, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- G. Aldosary, A. Nobah, F. Al-Zorkani, S. Devic, B. Mofteh, The Influence of a Modeled Treatment Couch on Dose Distributions in IMRT and RapidArc for High-Energy Photon Beams, Oral abstract, ROP Abstract 11, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- B. Mofteh, Roles and Responsibilities and education and training of medical physicists, IAEA Workshop on the Role of Medical Physicists in Radiotherapy, Manama, Bahrain, November 13, 2014.
- B. Mofteh, Advanced techniques in Radiotherapy: Stereotactic radiotherapy, IAEA Workshop on the Role of Medical Physicists in Radiotherapy, Manama, Bahrain, November 13, 2014.
- B. Mofteh, AAPM recommendation for linac QA, report 142, IAEA Workshop on the Role of Medical Physicists in Radiotherapy, Manama, Bahrain, November 14, 2014.
- B. Mofteh, External beam dosimetry: TRS398 and relative dose measurements for photons only, IAEA Workshop on the Role of Medical Physicists in

Radiotherapy, Manama, Bahrain, November 15, 2014.

- B. Mofteh, Radiation Protection, IAEA Expert Mission, Manama, Bahrain, September 9, 2014.
- B. Mofteh, KFSH&RC Biomedical Physics Department: Overview and R&D Activities, Noon Seminar Series 2014–2015, Medical Physics Unit, McGill University, Osler Amphitheatre, Montreal General Hospital, August 29, 2014.
- B. Mofteh, Medical Physics in Saudi Arabia: Past, Present, and Future, Continuing Education Course: World of Medical Physics, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16, 2014.
- B. Mofteh, Radiation in Medicine: Introduction, Continuing Education Course: Joint AAEA/KACARE/KFSH&RC Introduction to Radiation Medicine Continuing Education Course, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16, 2014.
- B. Mofteh, Radiation Oncology: Physics Aspects, Joint AAEA/KACARE/KFSH&RC Introduction to Radiation Medicine, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16, 2014
- B. Mofteh, Introduction to Radiation Protection, Continuing Education Course: Radiation Protection & Radiobiology, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16, 2014.
- A. Nobah, M. Mohiuddin, S. Devic, B. Mofteh, Treatment planning using passive grid block for spatially fractionated GRID radiation therapy, E-poster abstract E33-0186, ESTRO 33, Vienna, Austria, April 4–8, 2014.
- T. Amin, A. Azzam, R. Mahmood, Z. Hassan, H. Alselham, M. Hussain, B. Mofteh, Clinical Implementation of IntraOperative Electron Radiation Therapy (IOeRT) at KFSH&RC, Poster Session 19A: Radiation Oncology Track, Poster abstract 14, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- S. Devic, S. Aldelaijan, F. Alrumayan, M. Shehadeh, F. Alzorkani, J. Seuntjens, A. Almousa, B. Mofteh, Assessment of Radiochromic Film for Dosimetry of Low Energy Protons, Poster Session 19B: Medical Physics Track, Poster abstract 36, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- U. Mwidu, R. Mahmood, M. Hegazy, Z. Hassan, B. Mofteh, M. Neimatallah, Image Adapted High Dose Rate Brachytherapy (HDR) at KFSH&RC Based on GEC-ESTRO Guidelines, Poster Session 19B: Medical Physics Track, Poster abstract 38, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- F. Alzorkani, S. Aldelaijan, F. Alrumayan, M. Shehadeh, S. Devic, M. Alfatih, N. Maalej, B. Mofteh, Comparison Between Proton Beam Characteristics of a Radiopharmaceutical Cyclotron Using Havar and Kapton as a Beamline Window, Poster Session 19B: Medical Physics Track, Poster abstract 39, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- A. Naga, N. Hussain, B. Mofteh, Commissioning Experience of a Cone-Beam Computed Tomography System and Implementation of Image-Guided Radiation Therapy Technique, Poster Session 19B: Medical Physics Track, Poster abstract 44, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.

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- G. Aldosary, A. Nobah, F. Al-Zorkani, Slobodan Devic and Belal Mofteh, Influence of a Modeled Treatment Couch on Dose Distributions During IMRT & RapidArc Treatment Delivery, Abstract, Poster Session 1, Annual Scientific Meeting of the Canadian Organization of Medical Physicists (COMP), Banff, Alberta, Canada, 9–12 June, 2014.
- S. Aldelaijan, A. Nobah, S. Devic, N. Tomic, J. Seuntjens, B. Mofteh, Dosimetric assessment of state of the art image guidance procedures using radiochromic films, Poster abstract E33-0324, ESTRO 33, Vienna, Austria, April 4–8, 2014.

- M. Hussain, Z. El Taher, H. Alselham, B. Mofteh, Commissioning of Mobetron for Intra-operative Radiation Therapy, Poster Session 19B: Medical Physics Track, Poster abstract 45, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- M. Al Kafi, A. AlMousa, K. Rabaeh, A. Basfar, B. Mofteh, Patient Specific Quality Assurance Using 3D Polymer Gel, Poster Session 19A: Radiation Oncology Track, Poster abstract 47, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.
- F. Mahyoub, K. Al-Hadyan, S. Binjamaan, C. Lagarde, H. Al-Humidan, A., S. Elewisy, O. Noor, H. Mosallay, G. Sayed, G. Alsbeih, B. Mofteh, Radiation Monitoring of Radiation Workers in Saudi Arabia. Service Review 2006–2012, Poster Session 19D: Radiation Biology and Safety Track, Poster abstract 97, International Conference on Radiation Medicine (ICRM2014), Riyadh, February 16–20, 2014.

#### Technical reports/patents/others

- Ahmed A. Basfar, Belal A. Mofteh, Khalid A. Rabaeh, Akram A. Almousa, Novel 3D Polymer Gel Dosimeters Based on N-(3-Methoxypropyl) acrylamide (NMPAGAT) for Radiation Therapy Treatment Planning System, Patent submitted to USPTO July 2014.
- Ahmed A. Basfar, Belal A. Mofteh, Khalid A. Rabaeh, Akram A. Almousa, Method of using the novel polymer gel for magnetic resonance imaging (MRI) Validation, Patent (Identified by Attorney Docket Number: RIPLLC007.024CIP1. US Application number 13/892484 and Patent Assignment EFS ID: 18348740, Application No: 14194975) was received by USPTO on March 3, 2014.

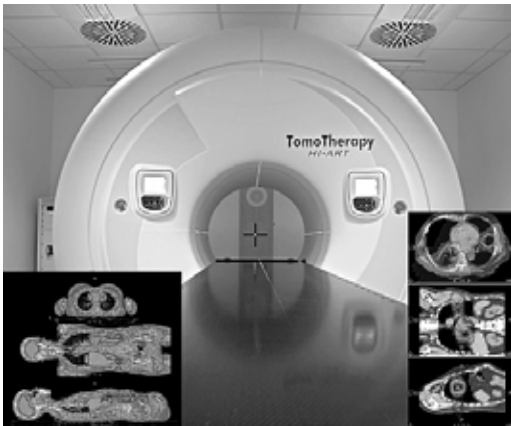
**FIVE MAJOR RADIOTHERAPY TREATMENT MODALITIES AT KFSH&RC**



Cyberknife



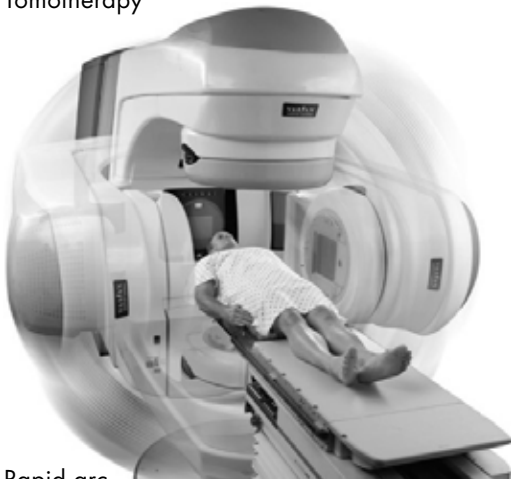
Nucletron HDR



Tomotherapy



Mobetron



Rapid arc



Intrabeam

IORT



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## RADIATION SAFETY OFFICE

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The main key target of the Radiation Safety Office (RSO) is to implement the radiation safety program at King Faisal Specialist Hospital and Research Centre. Its goal is to provide a radiation safe working conditions for all KFSH&RC personnel and patients, as well as the general public. This goal is achieved by ensuring compliance with national regulatory requirements and recognized international standards. The RSO coordinates and liaises with King Abdulaziz City for Science and Technology (KACST) and other national authorities on the purchase, use, transport and disposal of radioactive materials and radiation emitting equipment. It reviews and recommends to the Radiation Safety Committee (RSC) approval of authorizations for use of radioactive materials. The implementation of the KFSH&RC policies on radioactive waste management is the responsibility of the RSO. It provides technical consultation and services in the event of radiation incidents and emergencies. The RSO has a substantial commitment to training on radiation safety and it runs on-site lectures, presentations, and verbal instructions for users of radiation. The Office keeps and maintains documents and records pertaining to inventory of radioactive materials, radiation incidents, authorizations and other documents on radiation safety. The RSO collaboratively works with Health Physics Section of the Biomedical Physics Department. It maintains linkages with other KFSH&RC safety committees, national agencies and with international bodies such as IAEA.

**Fareed H. Mahyoub, MSc, MIPEM**  
HEAD

**Celestino Lagarde, BSc**  
**Ibrahim Al-Gain, BSc**

For the year 2014, the RSO successfully renewed the license of KFSH&RC for the radiation practices. The unit also renewed the license for the radioactive materials needed by the following departments: Nuclear Medicine, Radiation Therapy, Immunopathology, Gamma Irradiation Facility, Cyclotron & Radiopharmacy Department and Scientific Research from KACST. In addition to this, our license to import radioactive materials has now been renewed.

For RSO routine activities, the unit received a total of 375 imported radioactive materials. For outgoing radioactive materials, a total of 3000 were surveyed and approved for shipment. 300 spent Technetium-99 generators were disposed, a total of 600 leak testing were undertaken. A total

of 7 investigations were carried out on staff whose occupational doses exceeded the ALARA levels; 20 thyroid bioassays were performed.

The RSO also responded to at least 10 radiation incidents and provided technical consultations and assessments. About the radioactive waste management, a total of 120 drums were collected, surveyed, and stored in radioactive waste storage for decay.

In education and training, the RSO continuously provides lectures and technical training to students and medical practitioners throughout the year. At present, a total of 100 MOH employees are undertaking Radiation Protection Training in the department.

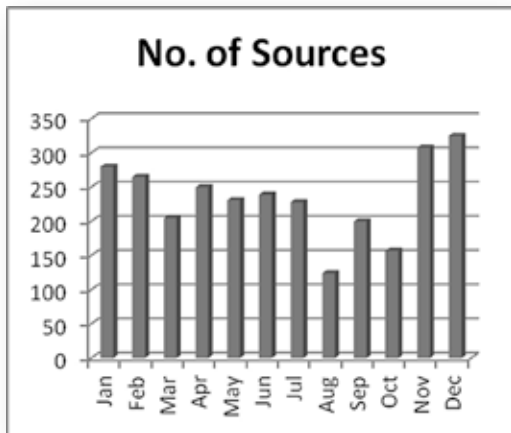


Figure 1. Graph showing the monthly out-going packages for year 2013.

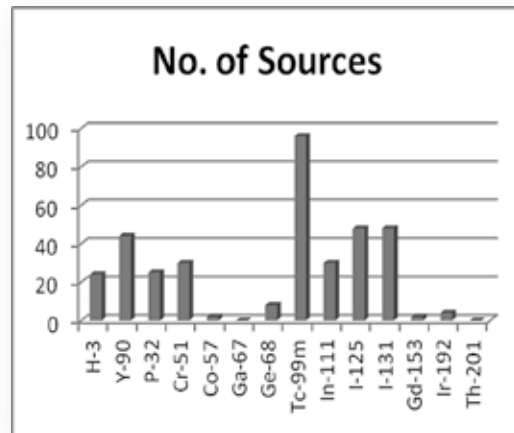


Figure 2. Graph showing the number of imported sources of radioactive isotopes in year 2013.

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## SECONDARY STANDARD DOSIMETRY LABORATORY

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In June 1988, the Secondary Standard Dosimetry Laboratory (SSDL) of the Biomedical Physics Department of KFSH&RC-Riyadh was accepted as a member of the joint IAEA/WHO network of SSDLs which was established in 1976 as a joint project between the IAEA and the World Health Organization (WHO). This network presently includes 80 laboratories and six (6) SSDL national organizations in 67 Member States, of which over half are developing countries. The SSDL network also includes 15 affiliated members (Primary Standard Dosimetry Laboratories, PSDLs) and 5 collaborating organizations; these supply support to the Network. One of the principal goals of the SSDL network is to guarantee that the dose delivered to patients undergoing radiotherapy treatment in the Member States is kept within internationally accepted levels.

The KFSH&RC's SSDL has continued to provide highly accurate services 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 the King Abdulaziz City for Science & Technology (KACST) 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.

**Fareed H. Mahyoub, MSc, MIPEM**

ACTING HEAD

**Heba Al-Humidan, BSc**

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**Mehenna Arib, PhD**  
(Visiting Consultant)

In 2014, the KFSHRC purchased for the SSDL 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 irradiation facilities were commissioned thanks to the assistance of a visiting consultant in September 2014 and in December 2014. This allowed the SSDL to upgrade and enlarge its calibration capabilities for radiotherapy, radiation protection and diagnostic radiology.

The present report covers the activities undertaken by the SSDL during the year 2014. Results of the commissioning of the new irradiation facilities are presented.

**ACHIEVEMENT AND ACTIVITIES**

**ROUTINE CALIBRATIONS**

During 2014, the SSDL provided calibration services in the field of radiation protection to 56 instruments for KFSH&RC, 46 instruments for government agencies and hospitals, 36 instruments for private hospitals, and 751 instruments for private companies (Figure 1a).

An overall number of 889 radiation-measuring instruments were calibrated, inter-compared and acceptance tested. These instruments include 770 survey meters and 119 pocket dosimeters (Figure 1b). The figure 3. shows the number of instruments calibrated per year since 2008.

In addition, the SSDL calibrated for the first time, 11 ionization chambers among which one plane parallel chamber in terms of absorbed dose to water (04 chambers for External Hospital, 03 for KFSHRC radiotherapy Department and the rest for the SSDL).

To ensure accuracy in its calibration, the SSDL participated in the IAEA and WHO annual postal dose audit for protection and therapy level calibration and obtained very satisfactory results.

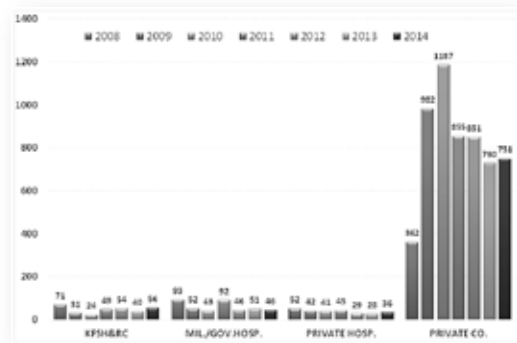


Figure 1a. Number of instruments calibrated for external facilities.

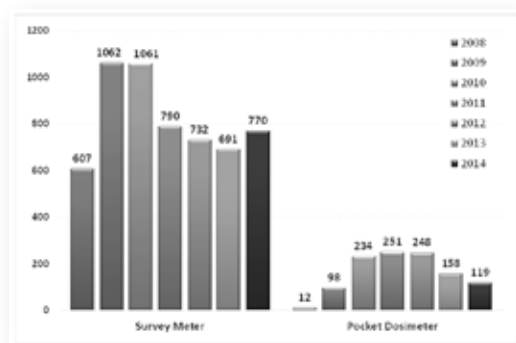


Figure 1b. Number of instruments calibrated for external facilities.

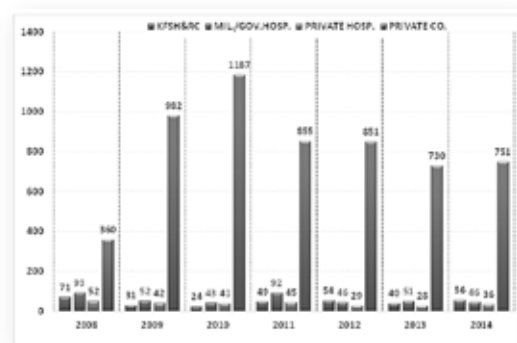


Figure 2. Number of instruments calibrated per year.

## DESCRIPTION OF THE COMMISSIONED FACILITIES

### Protection level calibration facility

The protection level calibration room is situated in the Basement of the Biomedical Physics Department. This bunker is L shaped and accommodates four irradiation facilities (Figure 3).

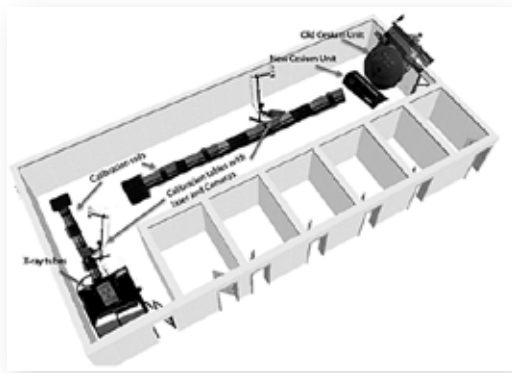


Figure 3. Protection level calibration bunker with two  $^{137}\text{Cs}$  and two X-ray irradiation units.

In the longest branch of the bunker, are installed two gamma irradiation facilities:

1. A multi-sources irradiator irradiation unit of type J.L. Shepard and Associates – NRC having six (06)  $^{137}\text{Cs}$  and one (01)  $^{60}\text{Co}$  sources with the following activities given at the date of October 27<sup>th</sup> 1981 (table 1). The third column gives the updated activities in Ci on 1<sup>st</sup> October 2014.

RADIONUCLIDE	INITIAL ACTIVITY (CI)	UPDATED ACTIVITY (CI)
$^{137}\text{Cs}$	270	126
	90	42
	30	14
	10	4.7
	3.3	1.5
	0.1	0.05
$^{60}\text{Co}$	10	0.13

In this type of irradiator (Figure 4), the sources are mounted on shielded operating rods which are moved from the completely shielded “off” position to the “irradiate” position behind an interlocked shield door. The interlocks are used to ensure that the source does not move into a position that, during normal use of the irradiators, may cause a radiation hazard to any individual. Bypassing or failure of interlock could cause persons to be exposed to high level of radiation. A survey meter or alarm meter must be used for determine the radiation level in the room while the irradiator with moving source (J. L. Shepherd irradiator) is operating.

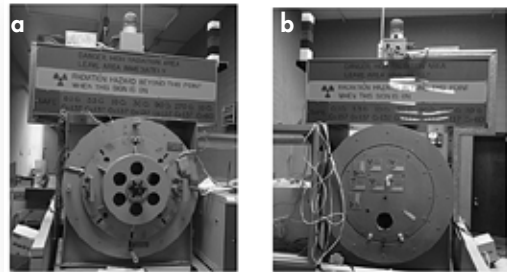


Figure 4. Multi-sources irradiator seen from rear (a) and front (b).

2. A new  $^{137}\text{Cs}$  irradiation (Figure 5) unit has been recently installed just below and in front of the old irradiator. The  $^{137}\text{Cs}$  source (activity 435 Ci (16.1 TBq) at the date of 25 December 2013) is moved from the shielded storage to the irradiation position using a piston driven by a compressor. When the irradiation times elapses, the source is taken back to the storage room. All the irradiation parameters are set-up on the remote control which is used also for controlling the old multi-sources irradiator.



Figure 5. New  $^{137}\text{Cs}$  irradiator installed in the Radiation protection Bunker and its remote control.

- On the other branch of the bunker, two x-ray units with maximum energies of respectively 320 kV and 160 kV, used respectively for radiation protection and diagnostic radiology calibrations, are installed one over the other so that their central beam axes are perpendicular to that of the  $^{137}\text{Cs}$   $\gamma$  beams (Figure 6).

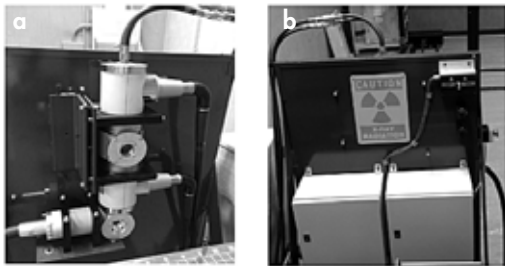


Figure 6. Two X-ray irradiation units: front (a) and rear (b) views.

### Ancillary Equipment

- Both irradiation systems (gamma and x-rays and also the therapy level gamma  $^{60}\text{Co}$  unit as we will see below) are associated with a Foss Therapy Services (FTS) Motorized Track System, which is a motorized system capable of moving a sample along an axis for experimentation and research testing. The table of the FT-60 Motorized Track System is powered by three legs capable of lifting 85 kilos at total distance of over 50 centimeters vertically. The FTS Motorized Track System is composed of high grade aluminum bases that support the table which runs along stainless steel shafts. The table is raised and lowered by three motorized legs. The table top incorporates an x/y grid for precise positioning of sample, instrumentation, etc. A thin layer of hard-coated polycarbonate covers the aluminum tabletop to minimize scatter;
- The track systems are equipped with two high-resolution cameras controlled with a remote control (zoom, focus) (Figure 7).

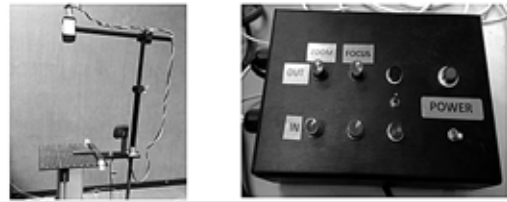


Figure 7. Camera and its remote control (Gamma and X-ray facilities).

- The bunker is equipped with two interlocks:
  - One on the swinging door giving access to the calibration room from behind the multisource irradiator;
  - One on the top of the door giving to the rear of the x-ray irradiators (Figure 8).



Figure 8. Door interlock.

- There are on the floor other interlock systems cutting any irradiation when walked on (Figure 9).

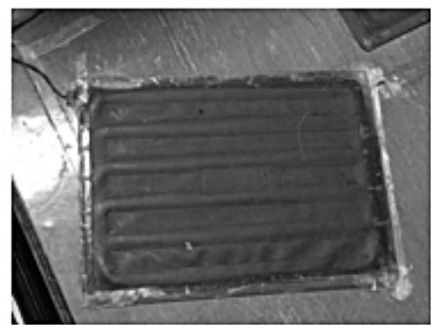


Figure 9. Floor detection system.

- One emergency switch off is available for the gamma systems (Figure 10).

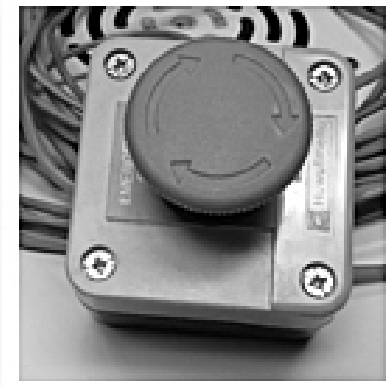


Figure 10. EMO.

- There are warning panels installed in the calibration bunker for safety purpose (Figure 11).



Figure 11. Safety warning panels in the calibration bunker.

- During the operation of the units, both doors are protected with two chains carrying panels displaying "CAUTION, RADIATION AREA. RADIATION beam ON, DO NOT ENTER" (Figure 12).



Figure 12. Warning Panels displayed on the doors outside the calibration rooms.

#### THERAPY LEVEL CALIBRATION FACILITY

The therapy level calibration bunker is situated on the first level in front of the Biomedical Physics Department. A new  $^{60}\text{Co}$  irradiation unit of type ELDORADO 78 is installed in vertical position giving a horizontal beam (See Figure 13). Due to the dimensions of the room, the irradiation is oriented towards the diagonal of the room.

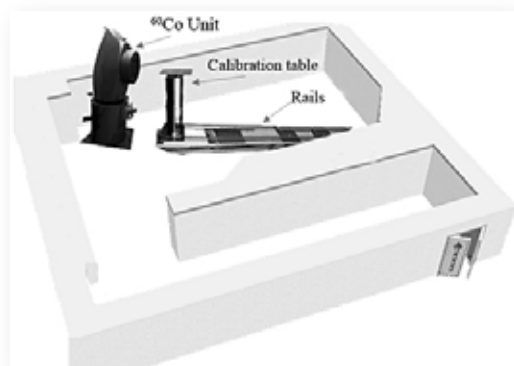


Figure 13. Warning Panels displayed on the doors outside the calibration rooms.

### Irradiation Facility

- The bunker is equipped with an ELDORADO 78 # 009 irradiator (Figure 14). The unit contains a <sup>60</sup>Co source which is a 2 cm diameter standard type C-146 made of plated pellets. The activity of this source is 192.4 TBq (5200 Ci) (Reference date: February 1<sup>st</sup> 2011). The theoretical source output measured in air at one meter is about 6734 mrem/h.

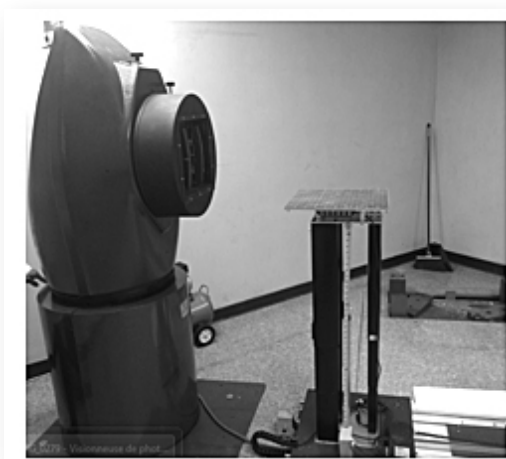


Figure 14. Irradiation unit and calibration tray.

- A remote control is installed in the control room allowing to set the irradiation time in hours, minutes and seconds (Figure 15).



Figure 15. Remote control.

- The irradiator is associated with a Foss Therapy Services (FTS) Motorized Track System, (calibration bench) called also Linear Positioning System (LPS) (see Figure 16). This LPS positions instruments, dosimetry badges and phantoms precisely and consistently within 1 mm. It has three axes of motion:



Figure 16. Motorized Track system.

- X: horizontal parallel to the beam: up to 2.5 meters;
- Y: horizontal perpendicular to the beam:  $\pm 18$  cm on the table
- Z: vertical course: 50 cm



Figure 17. Feed through hole.



Figure 18. Access door Locking system.

- There is one feed through hole tilted towards the interior of the bunker (Figure 17). This opening is used for cables passage;
- The shielded door is equipped with a manual locking system (Figure 18).
- The calibration room is supplied by the Hospital's air conditioning systems

## ANCILLARY EQUIPMENT

### Safety Interlock System

The safety interlock system consists of the following components:

- Two door interlocks: When the door is open, the power to the ELDORADO 78 is broken preventing source exposure (Figure 19).



Figure 19. Door interlocks.

- There are three Emergency Switch Off (EMO) buttons (Figure 20). One is located in the calibration room behind the  $^{60}\text{Co}$  unit (a). Another on the maze wall inside the room (b). The third one on the control console (c). When any EMO is pressed, the irradiator system is forced to its non-exposure state. The EMO buttons latch when pushed and must be manually reset before operation can resume. Only the remote console EMO button is clearly labelled (Figure 20.).

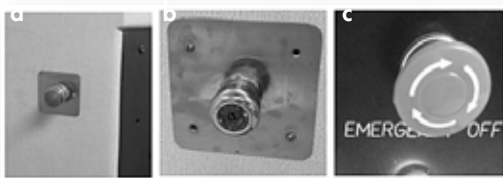


Figure 20. Emergency Switch-Offs (EMO).

### Warning Lights

The following warning lights which show the system status are available (Figure 21).



Figure 21. Warning lights.

1. A red light at the irradiator (a) is on when as long as the ELDORADO 78 is emitting radiations.
2. A green light on the wall facing the maze (b) is on when the key on the remote control is turned on. It turns to red when the beam is on;
3. There is a set of warning lights outside the calibration room besides the right door (c). The green light turns "on" when the key is "on". The red light in "on" during the irradiations and in between the orange light turns "on".
4. In addition to the warning lights, there are small lights on the remote control which follow the same logical behaviour (Green light on when the key is turned on, the red light on during irradiations). See Figure 22.



Figure 22. Warning lights on the remote control..

### **COMMISSIONING OF THE <sup>60</sup>CO THERAPY LEVEL CALIBRATION UNIT**

Safety assessment

- Safety Operation & Interlocks
- Radiation protection Survey

Ancillary equipment verification

- Alignment of the light beam
- Calibration of the digital distance indicator

Verification of the therapy level calibration unit

- Source positioning
- Timer Error (due to the movement of the source)
- Verification of the field size: Light and Radiation Field congruence
- Beam Profile
- Depth dose measurements
- Output measurements

Calibration of ionization chambers

- Establishment of calibration capabilities for radiotherapy dosimeters
- Determination of reference absorbed dose to water
- Calibration of cylindrical and plane-parallel ionization chambers in terms of absorbed dose to water
- Design of a calibration certificate to be issued by the SSDL for the newly established calibration service.

### **COMMISSIONING OF THE MULTISOURCES IRRADIATOR**

Safety assessment

- Safety Operation & Interlocks
- Radiation protection Survey

Verification of the Multisource irradiator unit

- Source positioning
- Timer Error (due to the rotation of the source)
- Verification of the air kerma and H\*(10) dose rates

Calibration of survey-meters

- Design of Excel worksheet
- Use of excel worksheet for calibrating survey meters

- Design of new calibration certificate

### **COMMISSIONING OF THE NEW 137CS IRRADIATOR**

Safety assessment

- Safety Operation & Interlocks
- Radiation protection Survey

Verification of the irradiator unit

- Verification of the distance indicator
- Source positioning
- Timer Error
- Verification of the air kerma and H\*(10) dose rates

Calibration procedure

- Establishment of new calibration procedure for survey-meters
- Design of an excel worksheet dedicated for calibration
- Testing of the new calibration procedure
- Design of a new calibration certificate

### **COMMISSIONING OF THE X-RAY UNITS (160 KV AND 320 KV)**

Safety assessment

- Safety Operation & Interlocks
- Radiation protection Survey

Verification of the irradiator unit

- Verification of the distance indicator
- Focal point positioning
- Timer Error
- Establishment of ISO 4037 qualities
- Establishment of some diagnostic qualities
- Measurement of absorbed dose reference rate for some qualities
- Calibration of survey-meters in x-ray beams

### **MISCELLANEOUS WORK**

Calibration of XRAD 320 X-ray irradiation unit

- Determination of the HVL
- Measurement of absorbed dose at the two reference distances (50 and 70 cm)
- Comparison with previous dose rates

## **ESTABLISHMENT OF A DRAFT FOR ISO 17025 QUALITY SYSTEM**

See the master record below

### **CONCLUSION**

- With the installation of the new irradiation facilities, the calibration capabilities of the SSDL has been considerably improved
- The SSDL of KFSH&RC continues to provide high accuracy in radiation measurements and dosimetry for all applications of ionizing radiation.
- The SSDL is ready for delivering outstanding calibration services not only for Kingdom end users but also for the region.



THE  
CARDIOVASCULAR  
RESEARCH PROGRAM



## CARDIOVASCULAR RESEARCH PROGRAM

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**T**he Cardiovascular Research Program (CRP) focuses on understanding molecular genetic and epigenetic mechanisms regulating cardiovascular diseases. The CRP has 3 major units focusing on epigenetic mechanisms in the diseased heart, the genetics of familial dilated cardiomyopathy and the role of a novel protein 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 with end-stage heart failure 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.

**Coralie I. Poizat, PhD**  
DIRECTOR

### MEMBERS

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Medical Student (Al Faisal University)

**Sarah Al Shalan**  
Undergraduate Student (Al Faisal University)

## RAC APPROVED RESEARCH PROJECTS

**PROJECT TITLE:** Epigenetic Regulation by Nuclear CaMKII in the Heart.

**ROLE:** Principal Investigator

**FUNDING:** KFSH&RC and KACST

**AIMS:** The Calcium/calmodulin-dependent protein kinase II delta (CaMKII $\delta$ ) is an enzyme that plays a central role in several major cardiovascular disorders including structural heart disease, arrhythmia and diabetes. In spite of a clear evidence for a role of CaMKII in heart diseases, the role of specific CaMKII isoforms, especially the ones enriched in cardiac nuclei, remain poorly understood. Data recently published from our laboratory allude to a novel function of nuclear CaMKII $\delta$  in the heart. We have discovered that CaMKII $\delta$  regulates pathological cardiac hypertrophy by a novel epigenetic mechanism involving post-translational modification of histone H3 by phosphorylation. CaMKII $\delta$  specifically signals to H3 at serine 10 during cardiac hypertrophy and this modification is critical for the activation of fetal cardiac genes that occur during pathological cardiac remodeling (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 uncovered that CaMKII $\delta$  directly couples calcium signals to chromatin *in vivo*. Using explanted hearts from patients in end-stage heart failure and CaMKII $\delta$ -deficient mice which are resistant to pathological stress, we showed that H3 phosphorylation is regulated by CaMKII $\delta$  after pressure overload hypertrophy. Upon haemodynamic stress, CaMKII $\delta$  is recruited and H3 is hyper-phosphorylated at hypertrophic promoters. 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 CaMKII $\delta$  as a new epigenetic modifier and revealing a new point of

control to design new strategies to treat a variety of cardiac disorders (Awad et al. *The Journal of Pathology*, 2014).

Under this project, we also investigated genetic causes of Dilated Cardiomyopathy (DCM). 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 ~ 70% of the cases are idiopathic and a significant number 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 have enrolled 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.

**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 that characterize 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 novel protein phosphatase (LMPTP) in the development of heart failure. Detailed functional and biochemical

studies performed in knockout mice deficient for the phosphatase (KO) revealed that the KO mice are resistant to long-term pressure overload hypertrophy and 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 the KO to pathological cardiac stress is in part due to activation of the insulin receptor beta and inhibition of 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. This study has been submitted for evaluation in a peer-reviewed journal.

In another study falling under this project, we investigated the role of the phosphatase in the development of 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 Dzimir). The association study performed in about 2,500 patients with coronary artery disease and the same number of normal individuals revealed several SNPs that conferred risk for low-level HDL and other SNPs implicated in obesity. One SNP located in the promoter region of the 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 3 (PI: F. Al Kuraya) and Project 4 (PI: N Al Tassan).**

**ROLE:** Co-Investigator

**FUNDING:** KFSH&RC

**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). These studies identified novel mutations in a core centrosomal protein that causes Ciliopathy in humans and a novel mutation in COL25A1 implicated in congenital cranial dysinnervation disorder. The two studies were published in the American Journal of Human Genetics.

#### **SELECTED ACHIEVEMENTS FOR 2014**

- Completed several studies resulting in oral presentations at local and international conferences and peer-reviewed manuscripts published in a high-impact factor journals.
- Awarding of a new grant from King Abdulaziz City for Science & Technology.
- 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.
- Formalized a new collaboration with Allosteric Therapeutics (USA) to test specific inhibitors in hypertrophic pathways.
- Trained medical students from Al-Faisal University, local high school students and undergraduate students.

## PRESENTATION AT LOCAL AND INTERNATIONAL CONFERENCES (LAST 2 YEARS)

### LOCAL

- Hakoun A, Al-Yacoub N, Al-Habeeb W and Poizat C. Identification of New Genetic Loci in Familial Dilated Cardiomyopathy. 4<sup>th</sup> 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. 4<sup>th</sup> 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.

### 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. 5<sup>th</sup> 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.

### PRESENTATION BY MEDICAL AND UNDERGRADUATE STUDENTS FROM ALFAISAL UNIVERSITY

- 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.
- AlShalan S, Mahmoud S and Poizat C. Expression Profiling of Epigenetic and Chromatin Remodelers Factors in Human Heart Failure. 5<sup>th</sup> Annual Research Day, Al Faisal University College of Medicine, 10 April 2014. 2<sup>nd</sup> place winner.
- Belhaj K, Wade F and Poizat C. Identification of Putative Substrates of A Protein Phosphatase in the Heart. 5<sup>th</sup> Annual Research Day, Al Faisal University College of Medicine, 10 April 2014.

### PEER-REVIEWED PUBLICATIONS (LAST 2 YEARS)

- Salma Mahmoud Awad, Mohammed S Al-Dosari, Nadya AlYacoub, Dilek Colak, Mustafa A Salih, Fowzan S Alkuraya and Coralie Poizat. Mutation in PHC1 Implicates Chromatin Remodeling in Primary Microcephaly Pathogenesis. *Hum Mol Genet.* 2013 Jun 1;22(11):2200-13. doi: 10.1093/hmg/ddt072. Epub 2013 Feb 14.
- Salma Awad Mahmoud, Muhammad Kunhi, Gillian H. Little, Yan Bai, Woojin An, Donald Bers, Larry Kedes and Coralie Poizat. Nuclear CaMKII Enhances Histone H3 Phosphorylation and Remodels Chromatin During Cardiac Hypertrophy.

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THE  
DEPARTMENT OF  
CELL BIOLOGY



## CELL BIOLOGY

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The Department of Cell Biology is completing its 3rd 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.

**Futwan A Al-Mohanna, PhD,**  
FIBiol, FRSC

CHAIRMAN

MEMBERS

**Camelia Touzint**

**Rita Sison**



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## XENOTRANSPLANTATION RESEARCH SECTION

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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.

**Futwan A Al-Mohanna, PhD,**  
**FIBiol, FRSC**

HEAD

MEMBERS

**Ranjit Parhar, PhD**

**Mohammed Quttainah, MD**

**Reem Al-Hejailan**

**Rana Al-Rabiah**

**Soad Saleh**

**Razan Bakheet**

**Azizah Al-Anazi**

**Sarah Al-Nassar**

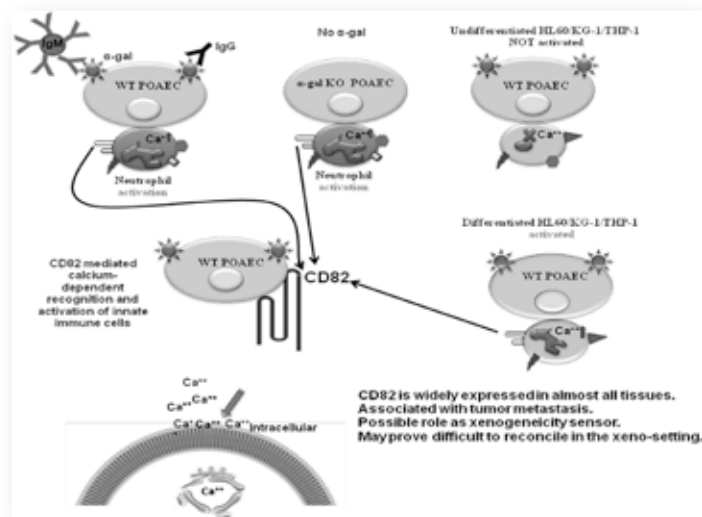
**Hussein Al-Hindias, DVM**

## ACTIVITIES

The Cardiovascular 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 xenoantigen independently of humoral responses associated with xenoreactive natural antibodies and complement that normally leads to hyperacute rejection of transplanted vascularized xenograft. We have recently identified a number of novel molecular moieties involved in the contact dependent and calcium mediated xeno recognition by innate immune cells using serial analysis of gene expression.

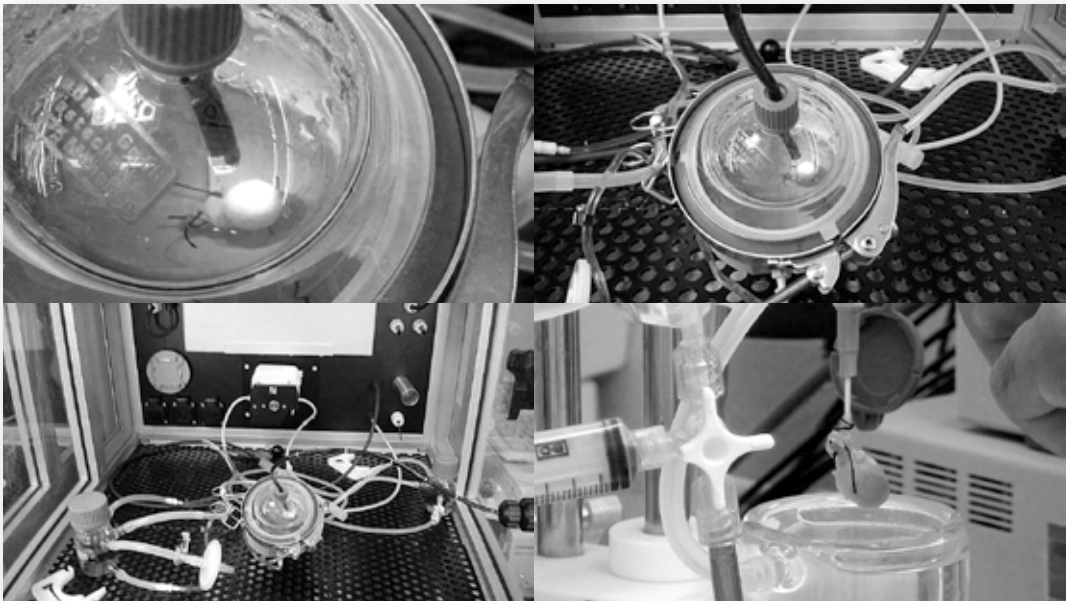
We identified a tetraspanin CD82 as the molecule for Gala, 3-gal-independent xeno antigen that play an important part in recognition and graft rejection mechanism. We reported that CD82 on innate immune cells acts as a major "xenogeneicity sensor" and open new avenues of intervention to making xenotransplantation a clinical reality.

A second line of research is the use of vaccinia virus complement modulatory protein VCP to block xenorecognition and complement activation. We have previously demonstrated the relative inhibition of xenorecognition and subsequent activation of porcine aortic endothelial cells by VCP. Our current work is focused on the production of large amounts of VCP in mammalian cells using cell factories. The work is moving toward the generation of a transgenic mouse expressing VCP. A third line of research in this section is organ regeneration where autologous hematopoietic stem cells (AHSC) were used to replace damaged areas in infarcted hearts. Despite its success in treating certain types of malignancies such as leukemia, clinical trials with Stem Cell Therapy in cardiovascular diseases have proved disappointing to date. Although relative improvement of cardiac output as a result of AHSC was seen in our animal model, we found no evidence to support the notion that autologous hematopoietic stem cells do not transdifferentiate into cardiac myocytes. Clearly more research must be done in order to answer important questions as to the future of Stem cell Therapy in Cardiovascular disease. We are currently working on reengineering a decellularized xenogeneic whole heart with intact vasculature and three-dimensional scaffold by recellularizing with EST in animal models.





Bioreactors



Decellularization



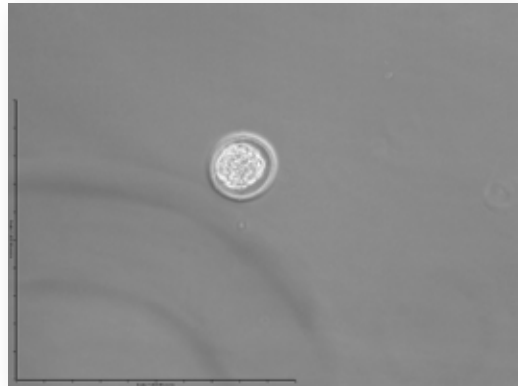
The decellularized protocols has also been optimized using sheep heart and kidney.



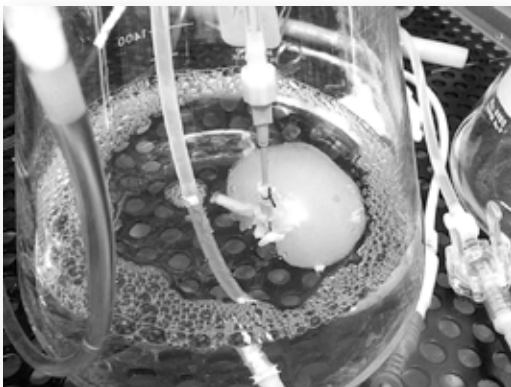
Decellularized Sheep Heart



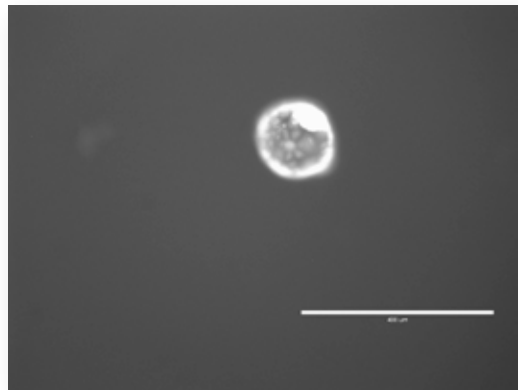
Decellularized Sheep Kidney



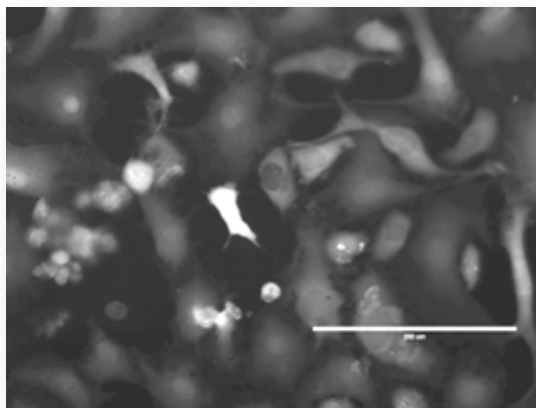
Mouse Blastocyst day 3.5



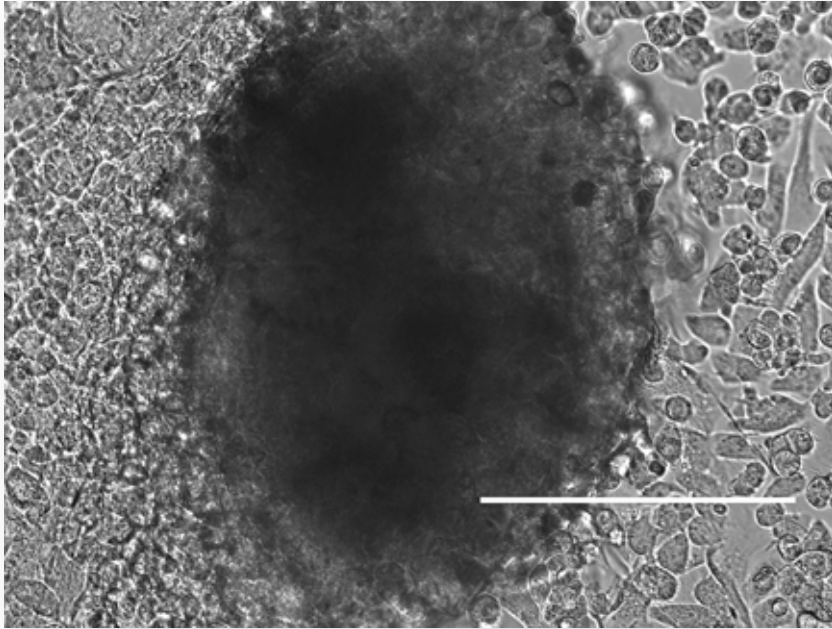
Mouse Blastocyst Isolation and to initiate using Embryonic Stem cell lines to Recellularized earlier Decellularized rat Heart.



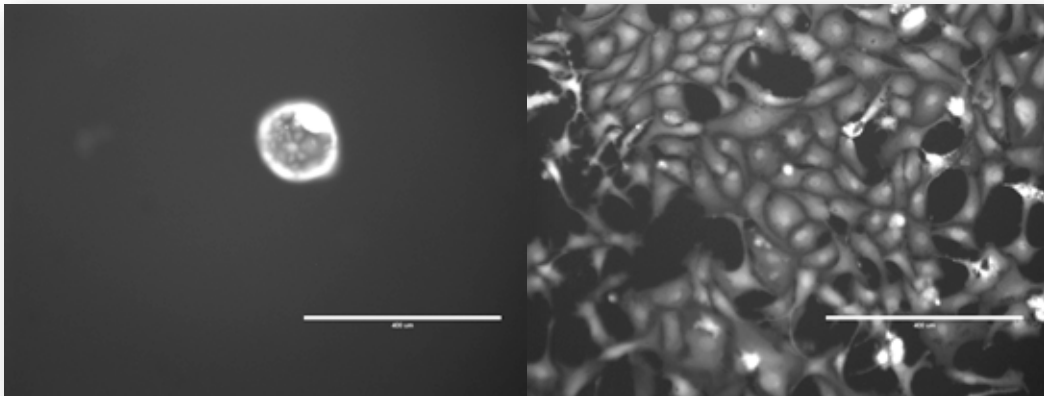
GFP C57/Bl6 Mouse Blastocyst day 3.5 Isolated and cultured



Inner Cell Mass Cell Isolated on day 10 to establish Embryonic cell lineage Cell line



Expansion Of Isolated Inner cell mass Embryonic Cells



A 3.5 day old blastocyst

Inner cell Mass cells

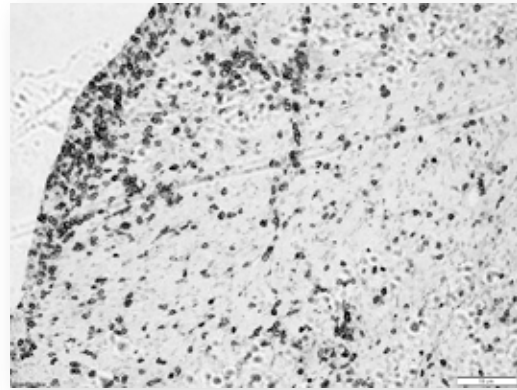
The various embryonic Stem cells of various lineages are used to recellularize earlier decellularized heart and study the different physiological parameters to evaluate the functionalities of these hearts.

**Heterotopic Heart Transplantation:** Allo-Transplantation and Xeno-Transplantation. We have established a heterotopic heart transplant model to evaluate the clinical potential use of VCP to protect both allo and xeno tissues in heart transplant model.

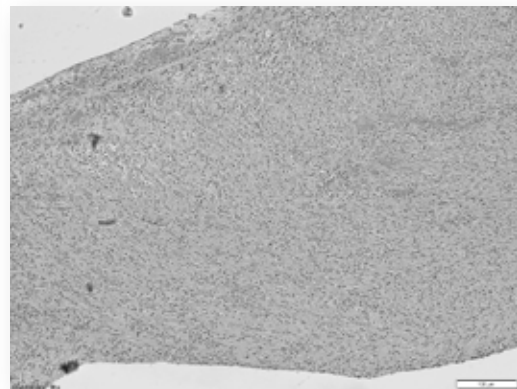


Heterotopic Transplanted Heart

#### HISTOLOGY OF REJECTED HEART



Allogeneic Rejected Rat heart on day 14 stained with anti-CD3 ab.



Allogeneic Rejected Rat Heart on day 14.

#### RAC AND KASCT APPROVED ( 2014 ) PROJECTS

1. **RAC# 2110011:** The use of Rat Embryonic stem cells in Decellularized Rat Heart. PI: Dr. Futwan Al-Mohanna. Co PI: Kate Collison, Ranjit Parhar, Reem Al-Hejailan, Falah Al-Mohanna, Abdullah Assiri, Zouhair Halees, Mail Al-Shahad, Mohanna Al-Mohanna and Sultan Al- Sedairy. In Progress.
2. **RAC # 2130-6:** Bio 2074-20 - Role of KLF3 in fatty acid  $\beta$ -oxidation: towards combating obesity." PI: Ranjit Parhar. Co PI: Futwan Al-Mohanna , Kate Collison, Sarwar Hashmi. In Progress.
3. **RAC# 2130-7:** BIO 1434-20 - IL-12 Gene Therapy of Thyroid Cancer in BRAFV600E Transgenic Mouse Model" PI : Yufei Shi Co PI: Minjing Zou, Ranjit Parhar. In Progress.
4. **RAC#2130-8:** BIO 2073-20 - Characterization of lacrimal and ocular mucosal immunity in the Arabian camel (*Camelus dromedaries* ). PI: Walter Conca. Co PI : Futwan Al-Mohanna, Ranjit Parhar, et al. In Progress.

5. **KASCT Project # 10-BIO956-20:** PI : M De Niro & F Al-Mohanna - Phenotypic and Gene Expression Profiling and their Correlation with Clinical Outcomes During the Development and Progression of Diabetic Retinopathy in Type 1 Diabetes Mellitus. In Progress.

#### PATENT

US-Patent Application No. 13/612,275 - 2015 Al-Mohanna FA et al

"Tetraspanin CD82 as a diagnostic and/or therapeutic module for Xenograft recognition and/or rejection" King Faisal Specialist Hospital & Research Centre.

#### PUBLICATIONS (FOR THE LAST 3 YEARS)

- Cancer: Is it linked to dysfunctional lipid metabolism? Hashmi S, Wang Y, Suman DS, Parhar RS, Collison K, Conca W, Al-Mohanna F, Gaugler R. *Biochimica et Biophysica Acta (BBA)* - General Subjects Volume 1850, Issue 2, Pages 352–364, February 2015.
- Kinetics of matrixins and cardiokines expression in an ovine model of heart failure and recovery. Mohammed Quttainah, Reem Al-Hejailan, Soad Saleh, Ranjit Parhar, Walter Conca, Bernard Bulwer, Narain Moorjani, Pedro Catarino, Raafat Elsayed, Mohammed Shoukri, Mansour AlJufan, Maie AlShahid, Abderrahman Ouban, Zohair Al-Halees, Stephen Westaby, Kate Collison, and Futwan Al-Mohanna, Submitted for Publication 2014.
- IL-12 Immunotherapy of BrafV600E-induced Papillary Thyroid Cancer in a Mouse Model. Ranjit S. Parhar, Minjing Zou, Futwan A. Al-Mohanna, Essa Y. Baitei, Abdullah M. Assiri, Brian F. Meyer, and Yufei Shi. Submitted for Publication 2014.
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- Regulation of lipoprotein assembly, secretion and fatty acid  $\beta$ -oxidation by Krüppel-like transcription factor, klf-3. Zhang J, Hashmi S, Cheema F, Al-Nasser N, Bakheet R, Parhar RS, Al-Mohanna F, Gaugler R, Hussain MM, Hashmi S. *J Mol Biol.* 2013 Aug 9;425(15):2641-55.
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#### ABSTRACTS PRESENTED

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- Alanazi A, Parhar R, Al-Hijailan R, Saleh S, Al-Halabi M, Inglis A, Conca W, Al-Jufan M, Collison K and Al-Mohanna F. Hypoxia alone is sufficient the release of leptin, VEGF and IL-6 from adipocytes. Complication of diabetes (X7 Keystone Symposia on molecular and cellular biology), page 78, March 23-28, 2014. Whistler, British Colombia, Canada.

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## DIABETES RESEARCH SECTION

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The global prevalence of diabetes currently stands at 387 million affected persons (8.3% 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). Additionally we were the first laboratory worldwide to report the finding that artificial sweeteners such as Aspartame may have the counter-intuitive effect of promoting glucose deregulation and weight gain.

**Kate S. Collison, PhD**

HEAD

MEMBERS

**Angela Inglis**

**Bernard Andres**

**Jennifer Thiam**

**Sherin M Shubin**

**Soad Saleh**

## **RAC-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

**OVERVIEW:** Two of the most widely-consumed food additives, Monosodium Glutamate (MSG) and Aspartame, contain the amino acids glutamate, aspartate and phenylalanine in the free (unbound) form. Consumption of these additives has been linked to neurological disturbances and gastrointestinal symptoms. Additionally, neonatal exposure to high doses of MSG results in a well-characterized hypothalamic obesity syndrome in rodent models, together with cognitive impairment. We have also demonstrated that neonatal exposure to Aspartame may result in a counter-intuitive weight gain and deregulation of glucose homeostasis, together with behavioral deficits. Both glucose homeostasis and many aspects of learning and memory are controlled by neuroendocrine circuitry in the hypothalamus/hippocampus, which contains an abundance of N-Methyl D-Aspartate (NMDA) receptors. We therefore aim to employ a specific competitive NMDA receptor antagonist in order to investigate further the role of NMDA receptors in Aspartame and MSG-induced metabolic / cognitive deregulation.

### **The Diabetic Retinopathy program**

Head: Michael DeNiro, DVM, MVM, MSc

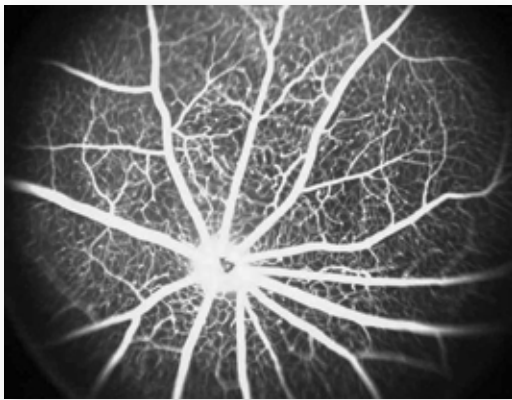
Members: Sally AlAhmar, MD (Research Technical Assistant), Areej AlQahtani, BSc (Research Technical Assistant), Modhi AlSalhani, BSc, MS (Research Technical Assistant)

**OVERVIEW:** 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.

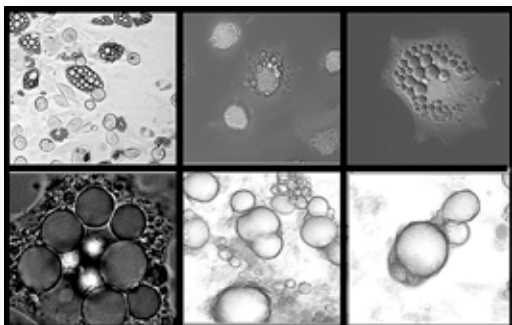
RAC No. 2100016 - Phenotypic and Gene Expression Profiling and their Correlation with Clinical Outcomes During the Development and Progression of Diabetic Retinopathy in Type 1 Diabetes Mellitus. Source of Funding: King Abdulaziz City for Science and Technology

(KACST). 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; and 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  $\beta$ -Oxidation: Towards Combating Obesity.**

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



## PUBLICATIONS

- Hashmi S, Wang Y, Suman DS, Parhar RS, Collison K, Conca W, Al-Mohanna F, Gaugler R. Human cancer: is it linked to dysfunctional metabolism? *Biochim Biophys Acta*. 2014, in press.
- Saleh S, Parhar RS, Al-Hejailan RS, Bakheet RH, Khaleel HS, Khalak HG, Halees AS, Zaisi 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 Immunology*. 191(5):2796-805, 2013.
- Hashmi S, Wang Y, Parhar RS, Collison KS, Conca W, Al-Mohanna F, Gaugler R. A *C. elegans* model to study human metabolic regulation. *Nutr & Metabolism (Lond)*. 2013 Apr 4;10(1):31
- Collison KS, Zaidi MZ, Makhoul NJ, Inglis A, Andres BL, Ubungen R, Saleh S, Al-Mohanna FA. Prediabetic changes in gene expression induced by aspartame and monosodium glutamate in Trans fat-fed C57BL/6J mice. *Nutr & Metabolism (Lond)*. 2013 Jun 19;10(1):44.
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- Collison KS, Zaidi MZ, Inglis A & Al-Mohanna FA. Letter-to-The-Editor, on "No effects of monosodium glutamate consumption on the body weight or composition of adult rats and mice" –further information. *Physiology & Behavior*, 2013, Feb 17;110-111:1-2.
- Collison KS, Makhoul NJ, Zaidi MZ, Al-Rabiah R, Inglis A, Andres B, Ubungen R, Shoukri M, Al-Mohanna FA. Interactive effects of monosodium glutamate and aspartame on glucose homeostasis. *BMC Nutrition & Metabolism*, (Lond). 2012 Jun 14;9(1):58.
- Collison KS, Makhoul NJ, Zaidi MZ, Saleh SM, Andres B, Inglis A, Al-Rabiah R, Al-Mohanna FA. Gender dimorphism in aspartame-induced

- impairment of spatial cognition and insulin sensitivity. *PLoS One*, 2012;7(4):e31570.
- DeNiro M and 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.
  - DeNiro M, Al-Mohanna FH, Alsmadi O, Al-Mohanna FA. The nexus between VEGF and NF $\kappa$ B orchestrates a hypoxia-independent neovasculogenesis. *PLoS One*. 2013; 8(3):e59021.
  - DeNiro M and Al-Mohanna FA. Zinc Transporter 8 [ZnT8] Expression is Reduced by Ischemic Insults: A Potential Therapeutic Target to Prevent Ischemic Retinopathy. *PLoS One*. 2012; 7(11):e50360.
  - DeNiro M and Al-Mohanna FA. Erythropoietin and anemia: biological markers that cannot be ignored in diabetic retinopathy. *Med Hypotheses*. 2012; 78 (4):555-6.
  - DeNiro M, Al-Mohanna FH, Al-Mohanna FA. Inhibition of reactive gliosis prevents neovascular growth in the mouse model of oxygen-induced retinopathy. *PLoS One*; 6(7):e22244.

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## ALLERGY AND AEROBIOLOGY

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### PROJECTS IN PROGRESS

“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) – Dr. SM Hasnain (Co-I), Dr. Sultan Al-Sedairy (PI).

This project deals with the monitoring of indoor allergens, toxic fungi and endotoxins present in the patient indoor environment. There appear to be no laboratory present 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. The ultimate goal of this project is to provide services to patients, institutions, hospitals, schools and individuals and thereby prevent and minimize the rising number of asthma and allergy patients 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.

Syed M. Hasnain, PhD, FACAAl,  
FAAAAI

HEAD

MEMBERS

Halima Al-Sini

Alanoud Al-Qassim

Abdulrahman Al-Sobhi

Mubarak Al-Enizi

Abdalmohsen Alanazi  
(Grant)

Cheryl Mijares  
(Grant)

**PROJECT COMPLETED IN 2014**

**PROJECT TITLE:** Allergotek Diagnostic and Therapeutic Program – NSTIP Project (Bioincubator\_3).

**PRINCIPAL INVESTIGATOR:** Sultan Al-Sedairy

**CO-INVESTIGATOR:** SM Hasnain

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).

**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.

**PRINCIPAL INVESTIGATOR:** Prof. A.S Al-Modaihsh

**CO-INVESTIGATOR:** SM Hasnain

A collaborative project with King Saud University, Project Number O8ENV319-O. Just concluded with sampling and analysis of allergenic pollen, fungal spores and falling dust particles in the environment of Riyadh at two different sites (Airport and Civil Defense Site).

**PROJECT TITLE:** Proteomics Analysis for Project Completed, Data Were Analyzed and 3 Manuscripts are Ready for Submission. 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 reveals 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.

**PROJECTS SUBMITTED IN 2014**

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

**PRINCIPAL INVESTIGATOR:** Prof. AR Al-Frayh

**CO-INVESTIGATOR:** SM Hasnain

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 further 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, and submitted to KACST for approval.

**PROJECT TITLE:** Immunophenotypic Characterization of Vernal Keratoconjunctivitis in Saudi Arabia.

**PRINCIPAL INVESTIGATOR:** Samar Al-Swailem

**CO-INVESTIGATOR:** SM Hasnain

Vernal keratoconjunctivitis results in significant ocular morbidity, and is much more common in the Saudi population than in Western populations. In addition to the quality of life burden on the patients and caregivers, some patients develop permanent corneal opacity, keratoconus and/or limbal stem cell deficiency, or complications

related to therapy such as corticosteroid-induced cataract or glaucoma, with permanent visual impairment. Insights into the pathogenesis of this disease may lead to more specific therapies such as immunotherapy. Given the relative rarity in other industrialized countries, it is unlikely that pharmaceutical companies will take the initiative in developing immunotherapy or other customized interventions to benefit the citizens of Saudi Arabia. Prospective cross-sectional study of patients with vernal keratoconjunctivitis. 254 patients and 67 controls will be enrolled. A comprehensive study of the pathogenesis of vernal keratoconjunctivitis in Saudi Arabia, with insight gained into the allergen hypersensitivity and markers of autoimmunity may provide opportunities for new therapies for this condition that is a particular burden in the region. This project was initiated in collaboration with King Khalid Eye Specialist Hospital to Wilmer Eye Institute, John Hopkins University, USA.

**PROJECT TITLE: Prevalence of Bronchial Asthma and its Relation to Indoor and Outdoor Aeroallergens in the Eastern Province of Saudi Arabia.**

**PRINCIPAL INVESTIGATOR: Hussain Al-Matar**

**CO-INVESTIGATOR: SM Hasnain**

To study the magnitude of asthma in the pediatric population of Eastern Province, to identify indoors and outdoors allergens and to examine the relationship between asthma and the identified allergens. Eastern Province is the area of interest for this research. Asthma prevalence study will be conducted in randomly selected school and pre-school children from both sexes. The selection will be based on "NEWS" terminology (North, East, West and South). Outdoors aeroallergens survey will be performed in 4 selected governorates/sampling sites in central locations between the selected schools. This project was submitted to NSTIP in collaboration with National Guard Hospital Affairs, Dammam.

## **PUBLICATIONS (FOR THE LAST THREE YEARS)**

- Hasnain SM, Akhter, T., Waqar, M.A. Airborne and Allergenic Fungal Spores of Karachi Environment and their Correlation with the Meteorological Factors. *Journal of Environmental Monitoring* published online: *J. Environ. Monit.*, 2012, 14 (3), 1006 - 1013.
- Hasnain SM Indoor Allergenic Profiles of Asthma in Saudi Arabia. 2012 International Conference on Environmental Pollution and Public Health, the Special Track within iCBBE (EPPH-iCBBE 2012). Shanghai, China.
- Hasnain SM, Al-Frayh, A.R., Subiza, J.L., et al. Sensitization to indigenous pollen and molds and other outdoor and indoor allergens in allergic patients from Saudi Arabia, United Arab Emirates and Sudan. *World Allergy Organization Journal*: June 2012 - Volume 5 - Issue 6 - p 59-65.
- Hasnain SM Environmental Allergen in Saudi Arabia, Asthma Symposium, 02 May 2012, King Saud Medical City, Children Hospital, Riyadh.
- Hasnain SM, Al-Frayh, A.R., Shakoor, Z. et al. The Development of Childhood Asthma: Risk Factors and Family History, European Academy of Allergy and Clinical Immunology (EAACI) Congress 2012, 16-20 June 2012, Geneva, Switzerland.
- Hasnain SM, Al-Frayh, A.R. Aeroallergenic Profiles and Increasing Prevalence of Asthma in the Middle-East". European Academy of Allergy and Clinical Immunology & World Allergy Organization (EAACI-WAO) Congress 2013, 22-26 June, Milan Italy.
- Al-Modaihsh AS, Mahjoub MO, Al-Qassim A, Al-Enizi M. Hasnain SM. "Qualitative and Quantitative Changes in the Prevalence of Aeroallergens in Riyadh Saudi Arabia". Asia Pacific Congress of Allergy, Asthma and Clinical Immunology (APCAACI) 2013, Taipei, Taiwan. *ALLERGY* (European Journal of Allergy and Clinical Immunology) Vol. 68, Suppl. 98 (2013): 52-A59 © John Wiley & Sons A/S.
- Alaiya, AA., Alsin, H.A., Gad-El-Rab, M.O., Hasnain SM. "Protein Profiles of Indigenous and Commercial Extracts of *Amaranthus* Pollen for the

Diagnosis of Allergy and Asthma Patients”, (RAC Approved #2140 252) – Accepted.

- Hasnain SM., Al-Qassim A., Hasnain S., Al-Frayh, A.R. “Emerging Status of Asthma, Allergic Rhinitis and Eczema in the Middle East”, (Submitted).
- Hasnain SM., Hasnain S., Al-Frayh, A.R. “Allergy and Asthma: Prevalence and Frequency of Inhalant Allergens in the Middle East”. (Submitted).

#### ABSTRACTS

- Hasnain SM., and Al-Qassim, A. Prevalent Airborne Pollen and Spores Allergens in Riyadh City, Saudi Arabia – Under an Allergy & Asthma Study Program, EPPH 2014, 12–14 April 2014, Shanghai, China.
- Hasnain SM., and Al-Frayh, A.R. Prevalence of HDMs, *Blatella* and *Periplaneta* allergens and their Clinical Impact on Allergic Patients in Saudi Arabia International Conference on Biological, Chemical and Environmental Sciences (BCES-2014), June 14–15, 2014, Penang, Malaysia.

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## CELL IMAGING AND MOLECULAR SIGNALING

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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).



THE CENTER FOR  
AUTISM RESEARCH (CFAR)



## CENTER FOR AUTISM RESEARCH (CFAR)

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The Center for Autism Research (CFAR) is working hard to establish a benchmark for diagnosis and early intervention as well as obtain research-reliability status and certification for training of other professionals who work with our targeted population. Since January 2012, we have conducted over 90 diagnosis procedures, consulted with 234 families with children with autism spectrum disorder and related disorders, and enrolled approximately 90 children in early intervention, therapeutic, and/or research studies. Also, we are proud to announce that we have 4 therapists who have obtained research-reliability and certification status in gold-standard diagnostic and early intervention models. Another important activity undertaken during the year was spreading awareness and knowledge related to the little understood disorder. The CFAR team conducted several workshops for families and specialists. Research projects and certification programs in applied technology, early intervention, and diagnosis are also underway. Most important projects include; LENA pilot study, Saudi Professional Development Program, Early Start Denver Model Training Program, Training and Certification in Applied Behavior Analysis, Functional Magnetic Resource Imaging, Genetics research, Developing and Adapting Touch-Based Electronic Devices for Diagnostic Interventional Uses, Characterizing Genetic Abnormalities in Autistic Spectrum Disorder and the Effect of Responsive Teaching of Mothers and Young Children with Autism in Saudi Arabia.

**Hesham Aldhalan, MD**  
DIRECTOR

## RAC APPROVED PROJECTS

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

Funded by KACST

This study is the first validation and experimentation study of the Language ENvironment Analysis (LENA) Systems in the Arabic language. This study is expected to pave the way toward more applications of this technology to aid the evaluation, characterization and treatment of a wide spectrum of language disorders, such as those associated with Autism. The study will also help in making this technology available for researchers and clinicians in Saudi Arabia and the Middle East. This research addresses two key strategic sub-tracks / fields of research identified in the strategic plan; neurological disorders and disability (Autism) which has an increasing incidence with no proven treatment apart from early intervention, which is the primary goal in our research. Ethical approval was obtained through King Faisal Specialist Hospital & Research Center's Office of Research Affairs (ORA). Autism patients were recruited through collaboration with Center of Autism Research at KFSH&RC and control (Typically Developing (TD)) are being recruited from the KFSH&RC's Day Care Center thorough active collaboration with the hospital Social Club. We have now 40 patients who have been recruited for each of the two groups (i.e. control and experimental). All data were analyzed with the help of our international collaborators. We expect reaching full patient recruitment within the time allotted. An abstract for 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 in extension of the project and it has been approved.

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

Funded by CFAR

The aim of this project is 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 will be 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, we will try to divide the groups using behavioral, neurocognitive and biological variables, which, according to scientific literature on the topic, may form the endophenotypes for autism. This project is in collaboration with Healthcare Belgium Foundation. All equipment for this project have been purchased and delivered. Technicians from Belgium group came and installed the equipment last December 2014. This project is expected to be launched by March 2015.

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

Funded by KFSH&RC

This project replaced the previous GCC CFAR project. This new modified project 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. We use the latest technology 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.

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

**Funded by CFAR**

The purpose of this project is to conduct a randomized control trial of the effectiveness of a commercially published, parent-mediated early intervention curriculum called Responsive Teaching. This project is a response to the King Salman Center for Disability Research (KSCDR) and Center for Autism Research (CFAR) research focus area of "Fostering advanced research and cutting-edge technology".

**PROJECT TITLE: Autism Spectrum Disorder Registry.**

**Funded by CFAR)**

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by varying degrees of delay or impairment in social interaction and communication with restricted and repetitive/stereotyped patterns. ASD is the world's fastest growing developmental disorder. There are no published data on the prevalence or incidence of ASD in Saudi Arabia. A major starting point for research in the area of epidemiology is establishing a registry. KFSH & RC is well based to start an ASD registry as it has a large referral-base with a catchment area covering the whole Kingdom as the main tertiary referral center. In addition, there are specialized clinics for ASD with a pediatric neuropsychology clinic that has evaluated and follows the largest cohort of ASD patients for the last 20 years. A hospital-based registry will help in organizing and mainstreaming data keeping and tracking of ASD patients seeing at various clinics. The data collected will shed light on the epidemiology of ASD in the entire country and will serve as the basis for future research. We plan to prospectively enroll

all patients who present for evaluation or follow-up in pediatric neurology, psychology, psychiatry, or speech pathology clinics who meet the current diagnostic criteria according to DSM-5.

### **SELECTED ACHIEVEMENTS**

- A. April Awareness campaign "For all children with Autism (April 2014).
  - 2 April 2014- Light it up Blue- The lighting up of many governmental buildings as well as CFAR and KFSHRC with the color blue. This initiative is intended to raise international awareness of autism as a growing public health crisis in support of both World Autism Awareness Day and Autism Awareness Month in the United States.
  - 2 & 3, 8, 9, 10 April 2014- Introductory and intermediate workshops for professionals and parents on Autism, diagnostics and intervention, play, as well as red flags and typical child development.
  - 4, 5, 11, 12 April 2014- Educational booths at local malls and various shopping centers-where specialists answered questions and gave consultations to concerned parents and interested students and therapists.
  - 19 April 2014- "Walk for Children with Autism"- A walk at King Fahad Stadium to spread awareness of the prevalence of the disorder and ways people can help. It included local and international business sponsors, local schools and centers, as well as siblings and family members of individuals with Autism.
  - 2 Days Sensory Workshop for Occupational Therapy, with the international speaker from California U.S.A. The objectives of these workshops were: To develop increase and understanding of and ability to plan and implement evidence based sensory based interventions that will support and enhance the child's occupational performance, to understand the components of a comprehensive assessment of sensory integration abilities and styles in individuals with ASD and how these functions influence on behavior and participation,

to identify common sensory and motor challenges in individuals with ASD and increase clarity of how they can be best addressed in interventions and to identify common sensory and motor challenges in individuals with ASD and increase clarity of how they can be best addressed in interventions. The first workshop had the number of 500 hundred attendees and the second workshop got 300 attendees.

- B. 2 Days Hanen Adopted Workshop (International speaker) Certification for this workshop is important for our specialists to be a trainer for parents on the strategies used to teach their children with autism on social and communication skills. Certification from this workshop is needed for the Occupational Therapist to be certified to do lectures and trainings for sensory integration and CFAR Senior Occupational Therapist got certified.
- C. Diamond Sponsorship for Saudi Epilepsy Society Meeting with Autism & Epilepsy track.
- D. International sponsorship for Research Project study about Autism Services for Children with Autism in Saudi Arabia.
- E. Intensive Training for Applied Behavioral Analysis Program (ABA) with international trainers from University of Nevada Reno– Aim to increase the Saudi society's capacity to deliver behavior analytic service for children with autism (ASD.)
- F. Memorandum of Understanding for Master's degree is in final review, this will help our Saudi ABA professional students to pursue their Master's degree in University of Nevada, Reno.
- G. Lecture for Master's and Doctoral program for Applied Behavioral Analysis has been given last September 2014.
- H. Two additional 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.
- I. Collaboration with University of North Carolina, we start to implement the Saudi National Centre for ASD program Development SCPD-ASD in school 51 as a collaboration with Ministry of Education to train teachers on how to use evidence based procedure.
- J. Got approved collaboration agreement with Mozzaz Corporation, to adapt and promote an assistive care application in the Arabic language with four phases: Assessment, Adaptation and Content Programming, Training, Support, and Consultation and Collaboration on Research.
- K. Two students were trained for Occupational Therapy from King Saud University.
- L. 4<sup>th</sup> International Pediatric Meeting.
- M. Grand round for the Neuro functional fMRI project.
- N. Provides trainings and lectures about autism for medical students, specialists and teachers for other Universities, schools and hospitals in Riyadh and Jeddah.
- O. Conducted LEARN workshop to train families with ASD children on how to maximize their communication, play and social skills their children (CFAR team)
- P. Conducted lecture of Occupational Therapy for King Saud University, conducted by CFAR staff Mr. Moneer Zakaria.
- Q. Conducted lecture of Autism Awareness for Al Sharq College.
- R. Autism Awareness lecture for Ministry of Education, conducted by CFAR staff Mr. Ahmed Jomaa.
- S. Lecture for Autism Early Detection for parents and specialist, conducted by international speaker Dr. Ann Cox.
- T. Lecture for What kind of Services Provided for Autism in the Kingdom of Saudi Arabia, conducted by Dr, Hesham Aldhalaan.
- U. Lecture for Autism Management and Services, conducted by Dr. Hesham Aldhalaan.
- V. Lecture for Toxoplasma-induced Metabolomics Changes: Basis for Novel Pathophysiology and Platform for Diagnostic Biomarkers of Autism and Epilepsy, conducted by Yasser Dabbagh.
- W. IPAD Applications Lecture for families and specialists, conducted by our international speakers from Mozzaz.

- X. Training Parents on Communication Skills, conducted by Lama Ohali
- Y. Two days lecture for male students & female students of King Saud University, conducted by CFAR specialists.
- Z. Lecture for Al Faisal School Elementary students about autism, conducted by Dr. Hesham Aldhalaan

#### **PUBLICATIONS:**

- Al-Owain, M., Kaya, N., Al-Shamrani, H., Al-Bakheet, A., Qari, A., Al-Muaigl, S., & Ghaziuddin, M. (2013). Autism spectrum disorder in a child with Propionic Acidemia. *JIMD Reports*, Mar; 7, 63–66.
- 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, M.J., 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 Spectrum 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 Disorder 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, 3<sup>rd</sup> International Conference on Disability and Rehabilitation, Riyadh, 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

**We are partner sponsors of:**

- Saudi Epilepsy Society Meeting – with Autism & Epilepsy track
- Applied Behavioral Analysis (ABA) training – competition of 1<sup>st</sup> semester theoretical practical studies.
- King Salman Center for Development Research (KSCDR), Online training for parents and children with autism spectrum disorder (ASD).
- International Research Project about Autism Services for Children with Autism in Saudi Arabia.

THE CLINICAL STUDIES AND  
EMPIRICAL ETHICS DEPARTMENT



## CLINICAL STUDIES AND EMPIRICAL ETHICS

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**T**he CSEED conducts clinical, environmental health, and empirical ethics studies and educates clinical research professionals. It also provides infrastructure for qualified clinical, environmental, and empirical ethics research by members of the KFSH&RC and aspires to be a resource for teaching / apprenticeship for clinical investigators at all stages of career development, a reference laboratory for environmental and pharmacokinetics studies, and a facilitator to promote optimal collaboration among basic laboratory researchers and clinical scientists. The CSEED is recognized as a bioequivalence Centre by the Saudi Arabian Ministry of Health and the Health Ministers of the Gulf Cooperative Council States among others.

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

CHAIRMAN

ADMINISTRATIVE SUPPORT

**Abdelraheem Abdel Galeel M.  
Ahmed**

**Maria Lourdes E. Bautista**



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## CLINICAL STUDIES

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The section conducts/facilitates the conduct of clinical studies including clinical trials and bioequivalence studies. Bioequivalence studies compare the speed and extent of absorption of two formulations of the same drug. They help ensure that locally-made generic drugs fulfill the bioequivalence requirements.

Educating and training clinical research professionals is at the heart of conducting clinical research that meets international ethics guidelines and scientific standards. The clinical studies section offers:

- a. Clinical Research Professionals' Course. A semi-annual three-weeks comprehensive course that consists of three modules:
  - Clinical Studies' Designs, Methods, and Analysis Module, accredited with 34 CME hours by the American Academy of Continuing Medical Education (AACME).
  - Experimental and Philosophical Approaches to Ethics: Application to Clinical Research Module, accredited with 29.50 CME hours AACME.
  - Clinical Research Activities Module, accredited with 25.25 CME hours by the AACME.
- b. Liquid Chromatography: Concepts and Hands-On Training Course. A semi-annual, one-week course accredited for 17 CME hours by the Saudi Commission for Health Specialties. It provides an indepth 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. It also covers basic pharmacokinetics analysis as well as laboratory safety and quality improvement program.

**Muhammad M. Hammami, MD,  
PhD**

HEAD

MEMBERS

**Syed N. Alvi, PhD**

**Eman Ali Al Gaii, CCRP, MHHA**

**Ahmed Yusuf**

**Rajaa Hussein**

**Reem Alswayeh**

**Nada Hashim**

**Saleh Al Dgither**

**Sophia Jehan Sahibbil**

**Abdelraheem A. Ahmed**

**Fadoma Ali Farah  
(Grant)**

**Basma Fayyad  
(Grant)**

**Chafica Eltabache  
(Grant)**

**Abdullah Abuarif**

**Nessrin Khodr  
(Grant)**

## FACILITIES

The clinical facility consists of a research clinic and a comfortable waiting area. The facility is staffed with qualified physicians, pharmacists, nurses, and clinical research coordinators. Research participants are provided with free access to emergency services and medical care at the King Faisal Specialist Hospital and Research Centre for research related adverse events. The facility is equipped with:

- Phlebotomy chair
- 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

The Bioanalytical Laboratory has been accredited by the College of American Pathologists (CAP)

since 2007 and offers a broad range of services, including, method development and validation, therapeutic drug monitoring, pharmacokinetic analysis, and bioavailability studies. It has developed and validated over 50 drug assays. It is equipped with:

- Five Waters Alliance HPLC Systems and multiple detectors: Ultraviolet (UV), Photodiode Array (PDA), Fluorescence (FL), and Electrochemical (ECD).
- Ultra Performance Liquid Chromatography (Aquity).
- Micro Mass Quattro Micro Tandem Mass Spectrometer (LC-MS-MS) System.

## RECENT ACTIVITIES

- Research Studies (Table 1)
- Educational Activities (Table 2)
- Publications (Table 3)
- Drugs assays developed and validated (Table #4)
- Fee-for-Service (Table #5)

1	Does Vitamin D improve glycemic control in type II DM ? A double-blind randomized controlled trial. RAC# 2101039 (closed). Abstract
2	Effect of Vitamin D Oral Supplement on 25 OH Vitamin D levels: A Randomized Controlled Trial. RAC# 2101041 (on-going). Abstract
3	Vitamin D Content in Fortified liquid milk in Saudi Arabia: A cross-sectional study. RAC# 2100014 (on-going). Abstract
4	Interaction Between Drug and Placebo Effect: Randomized Placebo-Controlled Trials may not be accurate in determining Drug Effect Size. RAC# 2111 001 (on-going). Abstract
5	Generic Formulations of Commonly-Used, Immediate-Release, Solid, Oral, Drugs in Saudi Arabia: Interchangeability & Post Marketing Quality. RAC# 2101100 (on-going). Abstract
6	Bisphenol determination urine submitted. RAC# 2141 021. Abstract

**Table 1.** RAC-approved Research Projects.

1	15 <sup>th</sup> Clinical Research Professionals' Course, 4 – 22 May, 2014
2	16 <sup>th</sup> Clinical Research Professionals' Course, 9 – 27 Nov, 2014
3	9 <sup>th</sup> Semi Annual Liquid Chromatography, 25 – 29 May, 2014
4	10 <sup>th</sup> Semi Annual Liquid Chromatography, 30 Nov – 4 Dec, 2014

**Table 2.** Educational Activities.

1	Ahmed Yusuf, Syed N. Alvi, and Muhammad M. Hammam. Rapid Determination of methotrexate level in human plasma by high performance liquid Chromatography. World Journal of Pharmacy & Pharmaceutical Science. 2014; 3 (10): 125-135.
2	Nada H. Binhashim, Syed N. Alvi, and Muhammad M. Hammami. A validated reversed phase HPLC assay for the determination of metronidazole in human plasma. World Journal of Pharmacy & Pharmaceutical Science. 2014; 3 (12): 32-41.
3	Reem Al-Swayeh, Syed N. Alvi, Muhammad M. Hammami. A validated HPLC method for the determination of ranitidine in human plasma: Application to bioavailability studies. Analytical Chemistry 2014; 15 (8).
4	Rajaa Farhan Hussein and Muhammad M. Hammami. Determination of gemfibrozil level and stability in human plasma by fully validated rapid HPLC analysis. World Journal of Pharmacy and Pharmaceutical Sciences. 2014; 3 (10): 174-185.
5	Rajaa Farhan Hussein and Muhammad M. Hammami. Determination of cephalexin level and stability in human plasma by fully validated rapid HPLC analysis. World Journal of Pharmacy and Pharmaceutical Sciences. 2014; 3 (12): 20 – 31.
6	Syed N. Alvi, Ahmed Yusuf, Eman Al Gaai and Muhammad M. Hammami. Rapid Determination of Ibuprofen Concentration level in human plasma by high performance liquid Chromatography. World Journal of Pharmacy & Pharmaceutical Science. 2014; 3 (8): 1767-1777.

Table 3. Publications.

1	Clarithromycin, full validation	LCMS/MS	0.2	Plasma
2	Amlodipine, full validation	LCMS/MS	0.5	Plasma
3	Fluconazole, Re-validation	HPLC	0.5	Plasma

Table 4. New Drugs assays developed and validated.

1	15 <sup>th</sup> Clinical Research Professionals' Course	79,800
2	16 <sup>th</sup> Clinical Research Professionals' Course	19,200
3	9 <sup>th</sup> Semi Annual Liquid Chromatography	12,000
4	10 <sup>th</sup> Semi Annual Liquid Chromatography	14,000
Total		125,000

Table 5. Fee-for-Service.

## RAC-APPROVED RESEARCH PROJECTS ABSTRACTS

**PROJECT TITLE:** Does Vitamin D Improve Glycemic Control in Type II DM ? A Double-blind Randomized Controlled Vial. RAC# 2101039:

Both vitamin D deficiency/insufficiency and type II DM/prediabetes are highly prevalent in Saudi Arabia. Vitamin D status has been negatively

associated with the presence of type II DM and glycemic control. A cause-effect relationship between vitamin D deficiency and glycemic control has not been established.

We plan to conduct a double blind, randomized, placebo controlled trial on the effect of vitamin D supplement on glycemic control in Type II DM.

300 adult, type II diabetics with stable HA1c between 6.5 and 8% and total 25 OH vitamin D level between 10-30 nmol/L will be stratified according to their body mass index:  $\leq 25$ ,  $>25$  to  $\leq 30$ ,  $>30$  to  $\leq 40$  kg/m<sup>2</sup> then randomized to receive 2000 or 5000 IU of vitamin D3 or a placebo for six months. Diabetes management will not be otherwise changed. Patients who become hypercalcemic or hypercalciuric or develop a HA1c above 8.5% or clinically unacceptable hypoglycemic episodes will be withdrawn from the protocol but will continue to be followed up.

The primary endpoint is the area under the curve (AUC) of HA1c. Secondary endpoints include AUC of systolic and diastolic blood pressure, weight, 25 OH vitamin D3, fasting blood glucose, and 2 hour post breakfast glucose, as well as fasting insulin to glucose ratio and the incidence of hypercalcemia and hypercalciuria. The primary endpoint of the three arms will be compared by ANOVA. Pair-wise comparison will be conducted by unpaired 2-tail t test.

The study will test the hypothesis that vitamin D deficiency and glycemic control in type II DM are causally related and that vitamin D repletion can improve DM control. The information obtained will be important for scientists in the field, managing physicians, and policy makers.

**STATUS/PROGRESS:** External funding by the National Plan for Science, Technology and Innovation (NPST) #-10-MED1362-20/total fund of SAR 1,957,919.00), Closed.

**PROJECT TITLE:** Effect of Vitamin D Oral Supplement on 25 OH Vitamin D levels: A Randomized Controlled Trial. RAC# 2101041.

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 IU D3; 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 ( $\leq 30$ ,  $> 30$  kg/m<sup>2</sup>) 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 Cmax and Tmax 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.

**STATUS/PROGRESS:** External funding by the National Plan for Science, Technology and Innovation (NPST) #-10-MED1363-20/total fund of SAR 2,000,000.00). In progress.

**PROJECT TITLE:** Vitamin D Content in Fortified Liquid Milk in Saudi Arabia: A Cross-Sectional Study. RAC# 2100014.

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. The samples were saponified over night at room temperature with a mixture of ethanol and potassium hydroxide (KOH). The digest was extracted with hexanes and washed with 5% ethanol in KOH. After evaporation, the residue was dissolved in acidic methanol and centrifuged. 100 µl of the clear solution was injected; and separation was achieved on Zorbax C18 column. The mobile phase, consists of methanol, acetonitrile and water that was used in a gradient elution mode. The eluents were monitored by photodiode array detector, with the wavelength set at 265 nm. No interference with endogenous components was observed. 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 was applied in assessing the levels

VD-2 and VD-3 in milk commercially available in the market of Riyadh, Saudi Arabia.

**STATUS/PROGRESS:** In progress.

**PROJECT TITLE:** Interaction Between Drug and Placebo Effect: Randomized Placebo-Controlled Trials May Not Be Accurate in Determining Drug Effect Size. RAC# 2111 001.

**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 as 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.

**STATUS/PROGRESS:** Ongoing.

**PROJECT TITLE:** Generic Formulations of Commonly-used, Immediate-Release, Solid, Oral, Drugs in Saudi Arabia: Interchangeability and Post-Marketing Quality, RAC #2101 100.

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 Cmax (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.

**STATUS/PROGRESS:** External funding by the National Plan for Science, Technology and Innovation (NPST) #10-BIO961-20/total fund of SAR 1,999,500.00). In progress.

**PROJECT TITLE:** Bisphenol determination urine submitted. RAC# 2141 021.

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 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.

**STATUS/PROGRESS:** Submitted for external funding.



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## EMPIRICAL ETHICS

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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.

**Muhammad M. Hammami, MD,  
PhD**

HEAD

MEMBERS

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

**Fadumo Sagal Shire**

## PUBLICATIONS

- Muhammad M Hammami, Eman A Al-Gaai, Yussuf Al-Jawarneh, Hala Amer, Muhammad B Hammami, Abdullah Eissa and Mohammad Al Qadire. Patients' perceived purpose of clinical informed consent. Mill's individual autonomy model is preferred. *BMC Medical Ethics* 2014, 15:2.
- Muhammad M Hammami, Yussuf Al-Jawarneh, Muhammad B Hammami and Mohammad Al Qadire. Information disclosure in clinical informed consent: "reasonable" patient's perception of norm in high-context communication culture. *BMC Medical Ethics* 2014, 15:3

## RESEARCH STUDIES

**PROJECT TITLE:** Preventive Interventions: Extent of Knowledge, Preferences, and Current Practices. (RAC# 2141 135).

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.

**STATUS/PROGRESS:** ongoing

**PROJECT TITLE:** Patient's Perception of Informed Consent: Function and Required Information. RAC# 2081 002.

**ABSTRACT-1:** Information Disclosure in clinical informed consent: "reasonable" patient's perception of norm in high-context communications culture.

**Background:** The current doctrine of informed consent for clinical care has been developed in cultures characterized by low-context communication and monitoring-style coping. There are scarce empirical data on patients' norm perception of information disclosure in other cultures. **Methods:** We surveyed 470 adults who were planning to undergo or had recently undergone a written informed consent-requiring procedure in a tertiary healthcare hospital in Saudi Arabia. Perceptions of norm and current practice were explored using a 5-point Likert scale (1=strongly agree with disclosure) and 30 information items in 7 domains: practitioners' details, benefits, risks, complications' management, available alternatives, procedure's description, and post-procedure's issues. **Results:** Respondents' mean (SD) age was 38.4 (12.5); 50.2% were males. 57.2% had  $\geq$  college education, and 37.9% had undergone a procedure. According to norm perception, strongly agree/agree responses ranged from 98.0% (major benefits) to 50.5% (assistant/trainee's name). Overall, items related to benefits and post-procedure's issues were ranked better (more agreeable) than items related to risks and available alternatives. Ranking scores were better in post-procedure respondents for 4

(13.3%) items ( $p < 0.001$  to  $0.001$ ) and in males for 8 (26.7%) items ( $p < 0.008$  to  $0.001$ ). Older age was associated with better ranking scores for 3 (10.0%) items and worse for one ( $p < 0.001$  to  $0.006$ ). According to current practice perception, strongly agree/agree responses ranged from 93.3% (disclosure of procedure's name) to 13.9% (lead practitioner's training place), ranking scores were worse for all items compared to norm perception ( $p < 0.001$ ), and post-procedure status, younger age, and lower educational level were associated with better ranking scores for 15 (50.5%), 12 (40%), and 4 (13.3%) items, respectively ( $p < 0.001$  to  $0.009$ ). **Conclusions:** 1) even in an overall high-context communication culture, extensive and more information is closer to benefits and post-procedure's issues than risks and available alternatives, 3) male, post-procedure, and older patients are in favor of more information disclosure, 4) male, older, and more educated patients may be particularly dissatisfied with current information disclosure. The focus and extent of information disclosure for clinical informed consent may need to be adjusted if a "reasonable" patient's standard is to be met.

**ABSTRACT-2:** Patients' perceived purpose of clinical informed consent: Mill's individual autonomy model is preferred

**Background:** Although informed consent is an integral part of clinical practice, its current doctrine remains mostly a matter of law and mainstream ethics rather than empirical research. There are scarce empirical data on patients' perceived purpose of informed consent, which may include administrative routine/courtesy gesture, simple honest permission, informed permission, patient-clinician shared decision-making, and enabling patient's self-decision-making. Different purposes require different processes. **Methods:** We surveyed 488 adults who were planning to undergo or had recently undergone written informed consent-requiring procedures. Perceptions of informed consent purpose (from norm and current practice

perspectives) were explored by asking respondents to rank (1=most reflective) 10 randomly-presented statements: "meaningless routine", "courtesy gesture", "litigation protection", "take away compensation rights", "inform patient", "make sure patient understand", "document patient's decision", "discover patient's preferences", "have shared decisions", and "help patient decide". **Results:** Respondents' mean (SD) age was 38.3 (12.5); 50.4% were males, 56.8% had  $\geq$  college education, and 37.3% had undergone a procedure. From the norm perspective, the least reflective statement was "meaningless routine" (ranked 1-3 by 2.6% of respondents) and the most reflective statements were "help patient decide", "make sure patient understand", and "inform patient" (ranked 1-3 by 65%, 60%, and 48% of respondents with median [25%,75%] ranking scores of 2 [1,5], 3[2,4], and 4[2,5], respectively). Compared to their counterparts, males and pre-procedure respondents ranked "help patient decide" better, whereas females and post-procedure respondents ranked "inform patient" better ( $p = 0.007$  to  $p < 0.001$ ). Age was associated with better ranking of "help patient decide" and "make sure patient understand" statements ( $p < 0.001$  and  $p = 0.002$ , respectively), which were ranked 1-3 by only 46% and 42% of respondents from the current practice perspective (median ranking score 4[2,6],  $p < 0.001$  vs. norm perspective for both). **Conclusions:** 1) the informed consent process is important to patients, however, patients vary in their views of its purpose with the dominant view being enabling patients' self decision-making, 2) males, pre-procedure, and older patients more favor a self decision-making purpose, whereas females and post-procedure patients more favor an information disclosure purpose, and 3) more self decision-making and more effective information disclosure than is currently practiced are desired. An informed consent process consistent with Mill's individual autonomy model may be suitable for most patients.

**STATUS/PROGRESS:** Completed. Two papers have been published by BMC Medical Ethics.

**PROJECT TITLE:** Written Versus Verbal Information in Consenting for Thyroidectomy: Patient Satisfaction and Information Retention. RAC# 2081 047.

**PROJECT DESCRIPTION:** A written informed consent is an ethical and legal requirement for surgical procedures. The information required for consenting can be provided in a verbal, unstructured format (traditional), or in a documented, structured format. The type of format may affect patients' satisfaction and the amount of information they retain. We plan to compare the two formats in regards to patient satisfaction and degree of information retention as well as perception of the role of consenting, time-cost, and practicality, in a randomized single-blinded study. Eligible patients requiring thyroidectomy will be block-randomized, to either format, at the time of scheduling for surgery. The structured format has been adopted from the literature. For the traditional format, the currently used generic form will be used, and the information to be verbally provided will be based on the recording of 3 traditional consenting episodes. Consenting using either format will be performed by one investigator. On the first post-operative outpatient visit, the participants will be informed about the study and asked to complete questionnaires on information retention, perception of the role of consenting, and patient's satisfaction, after obtaining their verbal consent. Preliminary questionnaires have been developed by the investigators and will be pre-tested on 5 thyroidectomy patients and 3 thyroid surgeons and modified accordingly. The questionnaires will be administered by an investigator blinded to participant's assignment. The two formats will be compared using the unpaired, two-tailed t-test. A Chi square test will be used to compare responses to individual statements (for patient satisfaction questionnaire). The results of the study are expected to provide empirical evidence on the efficacy as well as time-cost of the structured format for thyroidectomy (and indirectly for similar surgeries) and help physicians and policy makers improve patients' care and satisfaction.

**STATUS/PROGRESS:** Ongoing.

**PROJECT TITLE:** Saudis End-of-Life Priorities: Patterns and Extent of Sharing with Family Members and Physicians. RAC# 2081 057.

**PROJECT DESCRIPTION:** 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.

**STATUS/PROGRESS:** Ongoing.

**PROJECT TITLE:** Modeling Ethical Resolution: Mapping Points of Ethical Equilibrium RAC# 2060 004.

**PROJECT DESCRIPTION:** 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-maleficence, and justice) will be examined. The association of various demographic factors with the identified models and the effect of formal ethical education will be studied. 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 studies 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.

**STATUS/PROGRESS:** Ongoing.



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## ENVIRONMENTAL HEALTH RESEARCH

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The Environmental Health Research (EHR) continues to assess the extent of exposure to pollutants such as heavy metals, pesticides, phthalates, and polycyclic aromatic hydrocarbons in the general population with a particular reference to women and children.

**Iman A. Al-Saleh, PhD**

HEAD

MEMBERS

**Ghofran Qudaihi, PhD**

Started on 30 Nov. 2014

**Rola Elkhatib**

**Reem Al Rouqi**

**Inaam Aldoush**

**Mai Abdel Jabbar**

(Grant)

**Tahreer Al Rajudi**

(Grant)

## FACILITIES

The EHR section is well-equipped with modern analytical instrumentations such as:

- Zeeman atomic absorption spectrophotometer coupled to electro-thermal atomizer and vapor generator accessory.
- High performance liquid chromatography with UV/fluoresce/photodiode detector
- Mercury Analyzer DMA-80
- Gas chromatography with mass selective detector and coupled to CombiPAL auto-sampler in order to perform solid-phase solid-phase micro-extraction.

## RESEARCH STUDIES

**PROJECT TITLE:** Consequences of Oxidative DNA Damage Induced by Phthalates Exposure on the Outcome of *In Vitro* Fertilization Treatment. RAC#2131 024 (KACST # ARP-34-27) with a total fund of SR 1,296,400.

Phthalates are ubiquitous widely spread environmental contaminants worldwide. They have been used as additives in a variety of consumers, medical and personal-care products. There is a scientific and public concern about their possible health effects. Experimental studies showed that some phthalates are developmental and reproductive toxicants; particularly, on the male reproductive system in which oxidative stress has been suggested to be potential mechanisms involved. On the other hand, available human data on this topic remain vague and largely inconclusive. This prospective study is designed to look for the influence of phthalates exposure on the outcome of *in vitro* fertilization (IVF) treatment among Saudi couples. Our hypothesis is based on the assumption that exposure to phthalates might induce oxidative stress that could be responsible for the DNA damage in the sperm and oocyte that could lead to failed IVF. To achieve these objectives, we will recruit 1000 couples undergoing IVF treatment at

KFSH&RC to measure: (i) seven urinary phthalate metabolites, monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-iso-butyl phthalate (MiBP), mono-benzyl phthalate (MBzP), mono (2-ethylhexyl) phthalate (MEHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono (2-ethyl-5-oxohexyl) phthalate (MEOHP); and (ii) several oxidative stress biomarkers in seminal plasma and follicular fluid. A questionnaire will be also used to gather information on demographic, lifestyle and health factors that couples might be exposed and have an adverse effect on their reproductive function. Within this project, we will conduct a nested case-control study to assess the relation between exposure to phthalates and male infertility.

**STATUS:** The logistics of the project already prepared including the purchase of LC/MS/MS. The collection of samples will be started in April 2015.

**PROJECT TITLE:** Mercury Exposure During Lactation and its Effects on Saudi Infant's Neurodevelopment. RAC # 2080 049 (KACST # ARP-29-23) with a total fund of SR 1,050,000.

Mercury is a ubiquitous environmental toxin which has a wide range of adverse health effects in humans. It is found in three chemical forms: organic, inorganic and elemental (mercury). The sources of exposure are also markedly different for the three forms of mercury. Diet, especially fish and other seafood, is the main source of exposure of the general public to organic mercury. Dental amalgam is the most important source for elemental mercury vapor in the general population. Inorganic mercury compounds are known as "mercuric salts" which are sometimes used in skin lightening creams and as antiseptic creams and ointments. Exposure to mercury occurs typically by inhalation, ingestion or skin absorption. Mercury can be transferred prenatally to the developing fetus via the placenta or postnatally from breast milk to the nursing infant. Compare to adults, children are potentially more

susceptible to mercury due to differences in the stages of brain development and organ growth that occur during the fetal, infant, and childhood developmental periods. Literature concerning trans-placental and lactational mercury exposure and its health effects are few. The main objectives of the study are: (1) to evaluate postnatal exposure to different forms of organic and inorganic mercury and its association with delayed neurological development at different age groups; (2) to identify a culturally relevant neurodevelopment assessment tool that can be used in a general practice settings; (3) to examine the extent of lactational transfer of mercury taking into account mercury speciation in order to have a critical assessment of its adverse health effects; (4) to test the role of oxidative stress due to mercury exposure on neurodevelopment defects in infants by measuring biomarkers such as urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) and malondialdehyde (MDA); (5) to compare different mercury exposure indicators in order to evaluate various forms of mercury exposure and their predictive validity for assessment of accurate biological monitoring. For example, blood and hair will be used to determine organic mercury, while urine is suitable to estimate elemental and inorganic mercury; (6) to identify sources of mercury exposure through the use of exposure-assessment questionnaires; and (7) to identify a cohort of infants with high levels of mercury for further studies in the future. This cross sectional study will recruit 1250 lactating Saudi mothers and their respective infants who have reached the ages of 3 to 12 months old during routine visits to their respective Primary Health Care Units in Riyadh. Different biological samples such blood, urine, hair and breast milk will be collected for mercury analyses using the Atomic Absorption Spectrophotometer, coupled to Vapor Generator Accessory. Infant developmental status will be assessed by the use of Denver Developmental Screening Test (DDST) which has four developmental dimensions: gross motor, fine motor-adaptive, language, and personal-social. The Parents' Evaluation of Developmental Status (PEDS) is another fast and inexpensive method for detecting

developmental and behavioral-emotional problems will be also used which relies on parent's concerns about their infant's development. It is anticipated that this research project will provide relevant data to the public as well as health care community concerned with the impact of mercury on the health of young children especially with the recent concern over the use of thimerosal in vaccines and its possible association with autism and related disorders. Public health authorities could take the necessary legal and educational steps to restrict the availability of mercury containing products such as skin-lightening creams, thimerosal and dental amalgam.

**STATUS:** The project is completed successfully and the final report will be submitted to KACST in March 2015.

## EDUCATION ACTIVITIES

Trained 4 undergraduate students.

## PUBLICATIONS

- Al-Saleh I, Shinwari N, Mashhour A, Rabah A. Birth outcome measures and maternal exposure to heavy metals (lead, cadmium and mercury) in Saudi Arabian population. *International Journal Hygiene Environmental Health* 2014 Mar;217(2-3):205-18. doi: 10.1016/j.ijheh.2013.04.009.
- Al-Saleh I, Al-Rouqi R, Cercilia Angela Obsum, Shinwari N, Mashhour A, Billedo G, Al-Sarraj Y, Rabbah A. Mercury (Hg) and oxidative stress status in healthy women and its effect on birth anthropometric measures. *International Journal Hygiene Environmental Health* 2014 Apr-May;217(4-5):567-85. doi: 10.1016/j.ijheh.2013.11.001.
- Al-Saleh I, Elkhatib R. Analysis of phthalates residues in apple juices produced in Saudi Arabia. *Journal of Food Measurement and Characterization* 2014. 8 (4): 373-380. <http://link.springer.com/article/10.1007/s11694-014-9202-7>

### **ASSAYS DEVELOPED AND VALIDATED**

- Comet assay in seminal and follicular fluids.
- Organochlorinated pesticides in human milk by Gas Chromatography with Mass Spectrometer.
- Phthalates in perfumes by Gas Chromatography with Mass Spectrometer.

### **OTHER ACHIEVEMENTS**

1. Associate Editor, BMC Medical Ethics (Dr. Muhammad M. Hammami).
2. Associate Editor, International Journal of Hygiene and Environmental Health (Dr. Iman Al Saleh).
3. Best Poster Award (Dr. Alvi): 5<sup>th</sup> "World Congress on Bioavailability & Bioequivalence Pharmaceutical (R&D) Summit, Baltimore, Washington USA, Sept 29–Oct. 01, 2014 "Determination of 25-hydroxy vitamin D levels in type diabetic patients by high-performance liquid chromatography".

THE  
COMPARATIVE MEDICINE  
DEPARTMENT



## COMPARATIVE MEDICINE

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**T**he 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 and as well as to refine existing animal models while encouraging the use of alternatives to animal research.

**Abdullah Assiri, DVM, PhD**  
CHAIRMAN

ADMINISTRATIVE SUPPORT

**Janalie Narral**  
**Talal Alasmari**

This year, there is 26% increase in 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 342 participants including instructors, residents, and fellows were involved in these training activities, an increase of 64% from last year. This Year, there is 12% increase in animals numbers used for surgical procedures supporting over 500 surgical and endoscopic procedures that were carried out at the department for various research and training activities. The CMD hosted 110 Future scientists, AlRazi, Mawhiba and Alfaisal University students, an increase of 36%, in comparison to last year of 81 students,

The Laboratory Animal Services (LAS) at the main hospital and the KFNCRC provide specific pathogens free (SPF) laboratory animals to approved RAC projects. In 2014, the CMD-LAS has supported many research projects by providing over 7,000 animals which is translated into a 30% increase than 2013.

Moreover, the CMD Histology and Clinical Pathology and Diagnostics Laboratories have continued to support various biological samples processing for research and/or biosecurity purposes. This year, over 2,200 biological samples were processed and analyzed which benefited many investigators. The CMD Genotyping core services genotyped 2206 samples in the year 2014.

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.

#### HIGHLIGHTS

1. Establishment of Organ Transplant Research Section
2. Establishment of Laboratory Animal Facilities Environmental Screening procedure
3. Development of Brain Stroke Animal Model
4. Establishment of Immunohistochemistry Service
5. Initiating POC Genetically Modified Animal production and Cryopreservation Services

SN	ACTIVITIES	TOTAL NO.
1	Number of Approved Research Projects and Training Programs that were supported by CMD	72
2	Number of Small and Large Animals that were provided by CMD Laboratory Animal Services for various training and research programs	7107
3	Number of Biological Samples that were processed by CMD Histology and Clinical Pathology & Diagnostic Laboratories	2236
4	Number of Small and Large Animals used in surgical research training	360
5	Number of Genotyping Assays that were performed by the CMD Genotyping Core Facility for different transgenic and knockout mice	2206
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	342
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	110
8	Number of Publications that CMD staff authored/co-authored	2

**WORKSHOPS & TRAININGS**

1. Advanced Microsurgery "Hands-on" Course
2. Basic Surgical Skills
3. Advanced Gynecological Laparoscopy Training Course
4. Introduction on Using Laboratory Animals in Biomedical Research
5. Advanced Urological Laparoscopy Training Course
6. Alfaisal University Clerkship Program
7. Advances in Surgical Haemostasis Workshop
8. WFNS Skull Base Course
9. Future Scientist Program
10. Al Razi Program
11. Ibn Sena Program

**PUBLICATIONS OF CMD STAFF**

- Fascin is involved in the chemotherapeutic resistance of breast cancer cells predominantly via the PI3K/Akt pathway. Ghebeh H, Al-Khaldi S, Olabi S, Al-Dhfyhan A, Al-Mohanna F, Barnawi R, Tulbah A, Al-Tweigeri T, Ajarim D, Al-Alwan M.
- Control of histone H3 phosphorylation by CaMKII $\delta$  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.* 2014 Nov 25. doi: 10.1002/path.4489. [Epub ahead of print]

**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. Ministry of Agriculture
13. Qassim University
14. King Khalid University

**INTERNATIONAL COLLABORATIONS**

1. Emergent Bio-solutions

**LIST OF RAC ACTIVE PROJECTS**

SN	RAC NO.	PROJECT DESCRIPTION
1	2022 008	Microsurgery Intensive Hands-On Course
2	2032 002	Training of Surgical Residents in Bowel Anastomosis
3	2050 032	The Effect of Alpha Adrenergic Blockers on the Ureter: An In Vivo Study in the Dog
4	2060 016	Investigating the Role of the Actin-Bundling Protein (Fascin) in Regulating Dendritic Cells Migration and Breast Cancer Metastasis in Saudi Population
5	2070 023	Genetics of Vision Loss in Saudi Arabia
6	2080 009	Investigation of the Role of Stromal Fibroblasts in the Development of Breast Carcinoma: The Tumor Suppressor p16INK4A Protein as Target
7	2080 019	Transcriptional Regulation of TCR $\alpha/\delta$ Locus
8	2080 027	Study of the Anti-Cancer Properties of PAC (A Novel Curcumin Analogue) In Vitro and In Vivo
9	2080 029	Cyclooxygenases: Target for Epithelial Ovarian Cancer Prevention and Treatment
10	2080 031	Role of C-MET in Saudi Arabian Papillary Thyroid Carcinoma for Novel Therapy
11	2080 046	RoRyt Role in T Cell Development, Autoimmunity and Transformation
12	2080 052	Proteomic Analysis, Anti-Resorptive Properties and Tumor Cell Cytotoxicity of Osteodex in Bone Metastasis from Breast and Prostate Cancer
13	2090 014	Development of <sup>18</sup> F-Labeled Radiopharmaceuticals Beyond [ <sup>18</sup> F] FDG for Use in Oncology and Neurosciences
14	2090 028	Role of Excitatory Amino Acids in Trans Fat-induced Obesity, Dyslipidemia, Hepatic Steatosis and Cognitive Impairment
15	2100 003	Radiolabeled Bioactive Peptides: Potential Molecular Targeting Radiopharmaceuticals for Cancer Imaging and Therapy
16	2100 006	Making and Characterization of the Mouse Model for Hypogonadism, Alopecia, Diabetes Mellitus, Mental Retardation and Extrapyrimal Syndrome
17	2100 012	Percutaneously Adjustable Pulmonary Artery Band
18	2100 013	The Anti-breast Cancer Potential of Eugenol
19	2100 016	Phenotypic Anchoring, Global Gene Expression Profiling and Correlative Clinical Outcomes During the Development and Progression of Diabetic
20	2100 018	Study the potential anti-cancer properties of camel's urine
21	2100 023	Role of LMPTP in Cardiovascular Diseases
22	2100 024	Epigenetic regulation by Nuclear Calcium in the Heart
23	2102 001	Annual Pediatric Flexible Bronchoscopy Course (Animal Training Program)
24	2110 002	Development of Ga-68 Based PET-Radiopharmaceuticals for Management of Cancer and Other Chronic Diseases
25	2110 011	The Use of Rat Embryonic Stem Cells in Decellularized Rat Hearts
26	2110 013	Prolyl Hydroxylase Inhibitor Pretreatment in Cisplatin Induced Acute Kidney Injury Model
27	2110 021	Molecular Characterization of the Mechanisms in BRAF Splicing Variants and Pseudogene Mediated Signaling and Thyroid Tumorigenesis in Transgenic Mice
28	2110 025	Anti-Tumor Activity of XIAP Inhibitor Embelin on Mice Xenografts of Epithelial Carcinomas

SN	RAC NO.	PROJECT DESCRIPTION
29	2110 032	The miR29a-TTP axis regulation of RNA binding protein, HuR, and CXCR-4 in invasive breast cancer
30	2112 002	Microsurgery Training
31	2120 002	Research and Development of Lutetium - 177 based Radiopharmaceuticals for Targeted Radionuclide therapy of Cancer
32	2120 005	Duodenal Tubular Flap in the Surgical Repair of Choledochal Cyst
33	2120 006	Bio-screening of Herbs Liquids used in the kingdom for Anti-cancer Activity: Implications in Discovery of Anti-Cancer Agents
34	2120 015	Establishment of a living donor liver transplantation model in baboons (Pilot Study)
35	2120 016	Development and Optimization of Zirconium-89 Production and Clinical TF-PET/CT Imaging Protocols for Breast Tumor and Immunotherapy Planning
36	2120 019	Pharmacokinetics of Different Doses of Caffeine Mixed in Infant Formula: An Animal Pilot Study
37	2130 004	In the hand, can the flexor tendon heal to the volar plate?
38	2130 008	Characterization of Lacrimal & Ocular Mucosal Immunity in the Arabian Camel (Camelus Dromedarius): Implications for the Management of Sjogren's Syndrome
39	2130 011	Interactive Effects of Neonatal Exposure to Excitatory Amino Acids on Normal Metabolism, Learning & Memory: Role of N-methyl-D-aspartate receptors
40	2130 017	Characterization of Fascin Role in Stem Cell Function Knockout Mouse Model
41	2130 022	{18F} Radiopharmaceuticals / Radiotracers as Positron Emission Tomography Imaging Tools-Beyond {18F}-2-fluoro 2-deoxy glucose {18f} FDG
42	2132 001	3 <sup>rd</sup> International Difficult Airway Management Workshop
43	2132 002	Single Incision Laparoscopic Surgery (SILS) Training
44	2132 003	Establishing Heterotopic Heart Transplant in a Rat Model
45	2132 004	Advanced Urological Laparoscopy "Hands-on" Course
46	2140 001	The Role of the Immunomodulatory Molecule B7-H1 (PD-L1) in the Initiation and Maintenance of Cancer Stem Cells
47	2140 003	Cellular and Molecular Profiling of Primitive HSC Subsets in Umbilical Cord Blood & Bone Marrow Samples: Implications for Cell Therapy
48	2140 011	Role of T Cells in LPS-Induced Lung Inflammation and Dysfunction
49	2140 017	Unravelling the Molecular Link Between Obesity Breast Cancer: Role of Adipocytes & P16INK4A
50	2140 023	Investigation of Sprouty Family of Proteins in Thyroid Cancer Development and Progression
51	2140 031	Preventive and Therapeutic Potential of PAC on Thyroid Cancer
52	2140 035	Role of Epoxyeicosatrienoic Acids in Liver Regeneration
53	2141 037	Elucidate the Mechanisms through which Febrile-Range-Hyperthermia primes Neutrophils for Chemokine-Directed Trans-Vascular Egress
54	2142 001	Rapid, Simplified Training Technique for Heterotopic Cervical Heart Transplantation in Mice and Rat
55	2142 002	Advances in Surgical Haemostasis Workshop



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## LABORATORY ANIMAL SERVICES (LAS)

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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.

**Falah Almohanna, DVM, MSc**  
HEAD

MEMBERS — KFSH

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

MEMBERS — KFNCCC

**Ruben Delos Santos**  
**Wilfredo Antiquera**  
**Baltazar Caducio**  
**Mona Saleh**



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## EXPERIMENTAL SURGERY AND DIAGNOSTIC IMAGING SECTION

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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.

**Ra'afat Elsayed, DVM, MVSc**  
HEAD

MEMBERS

**Farraaj Alsamer**  
**Abdulrahman Alzuhaifi, MSc**  
**Ludivina Apilado, RN**  
**Sahar Salem, RN**



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## COMPARATIVE PATHOLOGY AND DIAGNOSTIC LABORATORY

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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.

**Abdullah Assiri, DVM, PhD**

ACTING HEAD

MEMBERS

**Asmaa Ali, DVM**

**Hala Ahmed**



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## COMPARATIVE FUNCTIONAL GENOMICS

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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.

**Abdullah Assiri, DVM, PhD**

HEAD

MEMBERS

**Bhavesh Mistry, MSc, PhD**

**Mohamed Rajab**

**Razan Abdullah**

**Maha Alanazi**



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## ORGAN TRANSPLANT RESEARCH SECTION

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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. Current investigations will develop innovative treatment modalities for patients with terminal organ failure.

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

HEAD

MEMBERS

**Dipok Dhar, MBBS, PhD**

**Mohammad Khan, MSc, PhD**

**Fatimah Alanazi**

**Abdullah Altuhami**



THE CYCLOTRON AND  
RADIOPHARMACEUTICALS DEPARTMENT



## CYCLOTRON AND RADIOPHARMACEUTICALS

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Cyclotron and Radiopharmaceuticals (C&R) Department performs two distinct functions in the Research Center: Radiopharmaceuticals manufacturing; and Radiotracer Research.

**Ibrahim Al-Jammaz, PhD**  
CHAIRMAN

ADMINISTRATIVE SUPPORT

**Jhonna L. Canicosa**  
**Nora B. D'Souza**

**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, more than 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 9001:2008 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 2014 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.

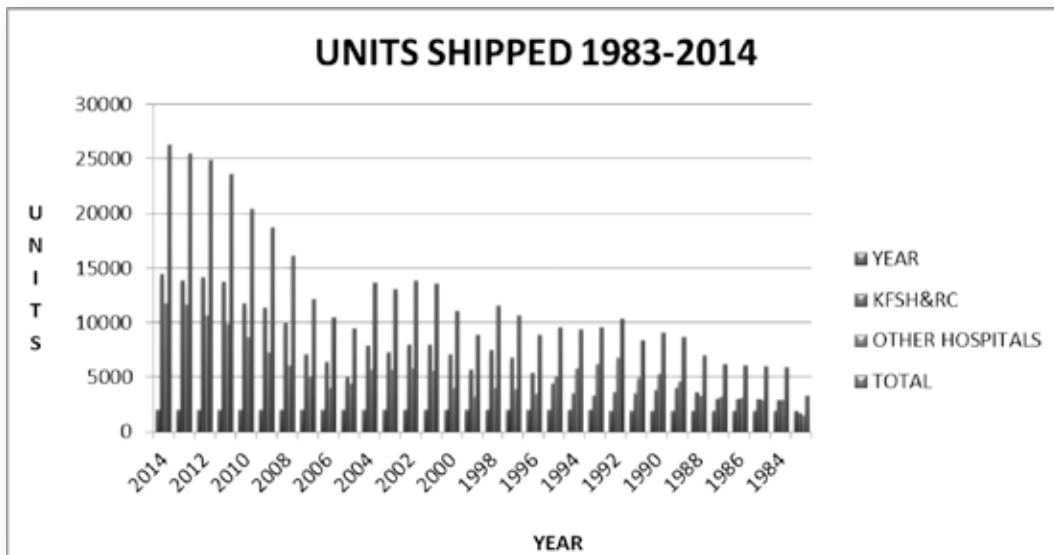
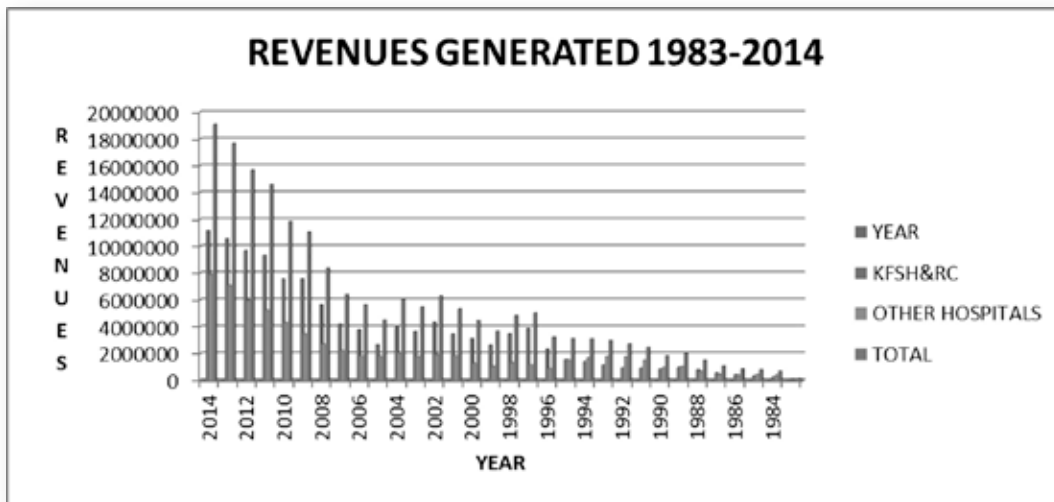
On the research and development front, achievements included not only the customary extramural research grant funds and large number of international publications and presentations, but also the production and quality assurance protocols for new radiotracers, and indigenously fabricated complex devices 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 2014:**

- Three new PET radiotracer, F-18 Choline, F-18 FLT and F-18 Sodium fluoride were made available for advanced PET imaging after rigorous protocols development, and two additional PET

radiotracers (F-18 FDOPA and [<sup>68</sup>Ga]DOTAOC-Octreotide) reached the pre-final stages of routine manufacturing;

- Acquisition of Nano-PET/CT imaging modality through extramural fund for Molecular Imaging research.
- Continual optimization and routine use of a new Krypton-81 target for routine patient use.
- Continual optimization and routine of a new Ammonia-13 target for routine patient use.
- Continuation of the production of Iodine-124 and radiolabeling of bioactive molecules.
- Continuation of the production of Zirconium-89 and radiolabeling of bioactive molecules.
- Radiopharmaceuticals distribution continued at the usual pace with improvement in reliability as the new equipment came into use. This year witnessed sizable increase in distribution of PET radiopharmaceuticals, in particular F-18 labeled FDG;
- Expertise and experience in radioisotopes and radiopharmaceuticals manufacturing in the C&R Department continued to be recognized by the International Atomic Energy Agency (IAEA, Vienna). In addition to becoming part of technical development projects with the Agency, several expert and consultation missions were undertaken by the senior staff in developing countries;
- 26292 units of radiopharmaceuticals distribution to 45 nuclear imaging centers in the Kingdom and abroad
- SAR19,106,703 revenues generated from distribution of radiopharmaceuticals manufactured in the C&RD
- >99% process success rate in manufacturing radiopharmaceutical products
- Achieved objectives of the ISO 9001:2008 Quality Management System, including customer satisfaction rate of ~96%
- Re-certification of ISO 9001:2008 Quality Management recertification



## RESEARCH PROJECTS

1. 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.
2. 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)
3. 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),.
4. 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).
5. 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)
6. National Production of Zirconium-89 for Tumour Imaging and Immunotherapy Planning.
  - KACST supported project # NPST 2120016 (SR 1,609,000).  
Investigator: I. AlJammaz (Co-PI) and S. Al-Yanbawi (Co-I)
7. 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)
8.  $^{18}\text{F}$ Radiopharmaceuticals/Radiotracers as Positron Emission Tomography imaging tools - Beyond  $^{18}\text{F}$ -2-fluoro-2-deoxyglucose ( $^{18}\text{F}$ FDG)
  - RAC # 2130 022 (SR 219,360).  
Investigator: M. Al-Qahtani (PI) and F. Al-Rumayan (Co-PI)
9. Remotely-Controlled Ammonia N-13 Target System for Cyclone-30 at KFSHRC.
  - RAC # 2130 030 (SR 256,000)  
Investigator: F. Al-Rumayan (PI) and M. Al-Qahtani (Co-I)
10. Intra-Operative Proton Radiotherapy (IOpTR), NCPT.
  - RAC# 2120026, (SR, 1,950,000),  
Investigator: F. Al-Rumayan (Co-PI)
11. Accelerator-based Alternatives to Non-HEU production of Mo-99/Tc-99m.
  - IAEA supported project # 16424 (SR 67,000).  
Investigator: I. AlJammaz (PI), F. Al-Rumayan (Co-I) and S. Al-Yanbawi (Co-I)
12. Development of Krypton-81 Target system for Cyclone-30.
  - RAC# 2100021, (SR, 70,000).  
Investigator: 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**

## PUBLICATIONS

- I. AlJammaz, B. Otaibi, N. AlHokbany, S. Amer, S.M. Okarvi: Development and Preclinical Evaluation of New  $^{68}\text{Ga}$ -NOTA-folate Conjugates for PET Imaging of Folate Receptor-positive Tumors. *Anticancer Res.* 34: 2014.
- I. AlJammaz, B. AlOtaibi, F. AlRumayan, S. AlYanbawi, S. Amer, S.M. Okarvi: Development and preclinical evaluation of new  $^{124}\text{I}$ -folate conjugates for PET imaging of folate receptor-positive tumors. *Nucl. Med. Biol.* 41: 457, 2014.
- I. AlJammaz, B. AlOtaibi, A. Abousekhrah, S.M. Okarvi: Rapid and one-step radiofluorination of bioactive peptides: Potential PET radiopharmaceuticals. *Appl. Radiat. Isotopes*, 91: 17, 2014.
- N. AlHokbany, B. AlOtaibi, S. Amer, S. M. Okarvi, I. AlJammaz: Synthesis and In Vitro and In

Vivo Evaluation of a New  $^{68}\text{Ga}$ -Semicarbazone Complex: Potential PET Radiopharmaceutical for Tumor Imaging. *Journal of Chemistry*, 2014.

- Dong Zhou, Mai Lin, Norio Yasui, Mohammed H. Al-Qahtani, Carmen S Dence, Sally Schwarz, and John A Katzenellenbogen (2014) "Optimization of the preparation of fluorine-18 labeled steroid receptor ligands 16alpha-[ $^{18}\text{F}$ ]fluoroestradiol (FES), [ $^{18}\text{F}$ ]fluoro furanyl norprogesterone (FFNP), and 16beta-[ $^{18}\text{F}$ ]fluoro-5alpha-dihydrotestosterone (FDHT), as radiopharmaceuticals", *J. Label. Compds. Radiopharm.*, 57, 371 – 377.

## ABSTRACTS

- S.M. Okarvi, I. AlJammaz: Chemical synthesis and evaluation of a  $^{68}\text{Ga}/^{177}\text{Lu}$ -labeled universal bombesin peptide ligand for targeting of bombesin receptor-positive tumors. *WFNMB*, 2014.
- S.M. Okarvi, I. AlJammaz: Synthesis, radiolabeling and *in vitro* and *in vivo* characterization of a synthetic peptide derived from the HER2/neu sequence for diagnosis and treatment of HER2/neu positive breast carcinoma. *WFNMB*, 2014.
- S.M. Okarvi, I. AlJammaz: Preparation and *in vitro* and *in vivo* evaluation of a novel peptide based on tumor-related human epithelial mucin (MUC1) as a potential breast cancer imaging agent. *WFNMB*, 2014.
- S.M. Okarvi, I. AlJammaz: Synthesis and *in vitro* and *in vivo* evaluation of a  $^{99\text{m}}\text{Tc}$ -labeled luteinizing hormone-releasing hormone (LHRH) peptide as a breast cancer imaging agent. *REGPEP*, 2014.
- S.M. Okarvi, I. AlJammaz: Design and development of a  $^{68}\text{Ga}/^{177}\text{Lu}$ -labeled universal bombesin peptide ligand for imaging and therapy of bombesin receptor-expressing tumors. *REGPEP*, 2014.
- S.M. Okarvi, I. AlJammaz: Preparation and evaluation of a specific peptide derived from the HER2/neu sequence: A potential candidate for the diagnosis and therapy of HER2/neu positive breast cancer. *EJNMI*, P968, 2014.
- S.M. Okarvi, I. AlJammaz: Development of a  $^{68}\text{Ga}/^{177}\text{Lu}$ -labeled universal bombesin peptide ligand for the diagnosis and targeted therapy of bombesin receptor-expressing tumors. *EJNMI*, OP525, 2014.
- S.M. Okarvi, I. AlJammaz: Synthesis and characterization of a novel peptide based on tumor-related human epithelial mucin (MUC1) as a potential breast cancer imaging agent. *EJNMI*, OP523, 2014.
- I. AlJammaz, B. Otaibi, S.M. Okarvi: Synthesis of Novel Gallium-68 Labeled Rhodamine: a Potential PET Myocardial Perfusion Agent. *EJNMI*, P214, 2014.
- S.M. Okarvi, C. Macatuno, I. AlJammaz: Solid-phase synthesis and evaluation of Lu-177 labeled HER2/neu-derived peptide: A potential radiopharmaceutical for the targeting of HER2/neu positive breast cancer. *KFSH&RC Annual Report*, 2014.
- Al-Qahtani, Mohammed, Al-Malki, Yousif, (2014) "A Comparison Study of Several Radioiodinated Intermediates for Labelling Short Peptides", presented at the 4<sup>th</sup>-International Nuclear Chemistry Congress, (4<sup>th</sup>-INCC), Maresias, Brazil, September 14–19, 2014, p109, *Abstract book*.
- F. Alrumayan, A. Alghaiith, Q. Akkam, A. Marsood and M. Al-Qahtani, (2014), "Development of [ $^{13}\text{N}$ ] Ammonia target for Cyclone-30 at KFSH&RC", 15<sup>th</sup> International Workshop on Targetry and Target Chemistry (WTTTC15), Prague, Czech Republic, 18–21 August, 2014, *Book of Abstract p 123*.
- Yousif Al-Malki and Mohammed Al-Qahtani (2014), "Evaluating radiolabeled peptides that has a potential as angiogenesis imaging radiotracers", 2013 *KFSH&RC Annual Research Report*, April 16–17.
- Marsood Ahmad, Surendra Nakka,, Abdulla Al-Swaiyilah and Mohammed Al-Qahtani (2014), "Our experience in Production of 18F-FDG; Past two decades", 2013 *KFSH&RC Annual Research Report*, April 16–17.
- F. Alrumayan and M. Al-Qahtani, "In-target Production of [ $^{13}\text{N}$ ]Ammonia Using High Energy Proton Beam", (2014), presented in the 3<sup>rd</sup> International Conference on Radiation Medicine (ICRM2014) held in KFSHRC, Riyadh, Saudi Arabia. 16–20 Feb 2014.

- N. Surendra, F. Alrumayan, A. Algaith, M. Ahmed and M. Al-Qahtani (2014), "Improving In-target production of [<sup>13</sup>N]-Ammonia using high energy proton beam", presented in the 3<sup>rd</sup> International Conference on Radiation Medicine (ICRM2014) held in KFSHRC, Riyadh, Saudi Arabia. 16–20 Feb 2014.
- F. Alrumayan, et. Al., "Development of a Visualization System for Charged Particles Shapes Superimposed on the Waveform of the Cyclotron Frequency", 23<sup>rd</sup> conference on Application of Accelerators in Research and Industry, 2014, May 25–30, San Antonio, Tx
- Ibtesam Badhrees, F. Alrumayan " The Perspectives of the Boron Neutron Capture Therapy-Clinical Applications Research and Development in Saudi Arabia" 23<sup>rd</sup> conference on Application of Accelerators in Research and Industry, 2014, May 25–30, San Antonio, Tx
- B. Mofteh, F. Alrumayan, S. Aldeljan, M. Shehadeh, F. Alzorkany, J. Seuntjens, M. Al shabanah and S. Devic, "Feasibility Testing Intra-operative Radiation Therapy Using Low Energy Proton" International Conference in Radiation Medicine, Riyadh 2014.
- F. Al Zorkani, S. Aldeljan, F. Alrumayan, M. Shehadeh, S.Devic, M.Alfatish, N.Maalej and B. Mofteh, " Comparison Between Proton Beam Characteristics of a Radiopharmaceuticle Cyclotron Using Havar and Kapton as a Beamline Window" International Conference in Radiation Medicine, Riyadh 2014.

# THE DEPARTMENT OF GENETICS



## THE DEPARTMENT OF GENETICS

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**D**uring 2014 the Department of Genetics was able to leverage its participation in the Saudi Human Genome Program to accelerate research in rare Mendelian disorders. Involvement in this program and establishment of the sequencing and informatics infrastructure has been a strong contributing factor towards the departments publication of over 60 high quality manuscripts related to hereditary disease and disease susceptibility. It is fair to say that KFSH&RC is now a world leader in rare diseases research. An academic highlight of 2014 was the recognition of Professor Fowzan Alkuraya who was awarded the prestigious Prince Salman Award for Disability Research.

**Brian Meyer, PhD**  
CHAIRMAN

ADMINISTRATIVE SUPPORT

**Lilia Fernandez**  
**Ralyn Alma O. Castillo**  
**Maritess Santiago**

Other academic achievements and highlights are as follows:

1. Over 60 high quality publications related to hereditary disease and disease susceptibility
2. Departmental scientists are engaged in more than 20 externally funded research grants totaling in excess of SAR 40 million.
3. Identification of 69 recessive genes not previously associated with neurogenetic disorders.
4. Demonstration of the value of molecular karyotyping for neurocognitive phenotypes in 584 patients
5. Identification of a novel gene (COL25A1) associated with Congenital Cranial Dysinnervation Disorder.
6. Identification of a novel gene (DEAF1) associated with white matter disease, intellectual disability and microcephaly.
7. Deciphering the molecular genetic basis of movement disorders in more than 50 patients from KFSHRC.
8. Identification of the molecular basis of hereditary deafness in more than 100 families from KSA.
9. Identification of a novel gene associated with chronic inflammatory syndromes such Juvenile Rheumatoid Arthritis (JRA) and Crohn's Disease.
10. Description of concomitant mutations of RAS, RET/PTC or BRAF mutations in Papillary Thyroid Carcinoma.
11. Analysis of over 300 cases of inherited Primary Immune Deficiency

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.

The Department of Genetics is also heavily engaged in service work undertaking the molecular genetic analysis, prenatal testing and newborn screening. Our core facilities continue to be the "engine room" for both research and service work. Core activities include DNA extraction, oligonucleotide services, genotyping, expression analysis, molecular karyotyping, Sanger sequencing, Next Generation Sequencing and Bioinformatics. Our training and education activities have included hosting of a large number of trainees ranging from gifted students, science and medical graduates to clinical fellows.

Given the extensive research and service activities of the department, our investment in training and development and the introduction of new technologies, we are well placed technically and academically and can look forward greater success in the year to come.

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## BEHAVIORAL GENETICS RESEARCH UNIT

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The main objective of the unit is to explore the molecular basis of complex disorders focusing mainly on multiplex families where trait segregates and also investigate sporadic single cases, with the aim to improve clinical diagnosis, genetic testing and counseling for affected individuals and families in Saudi Arabia.

The main interest in our laboratory is to identify novel causative and predisposing genes/mutations using a combination of homozygosity mapping, candidate gene screening and next generation sequencing and characterizing these mutations functionally in order to understand the mechanisms of development of the disorder.

**Nada Al Tassan, PhD**  
HEAD

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 Yamni**  
Alfaisal student

MSC STUDENTS

**Faten Al Naemi**  
**Loulia Akras**

## LIST OF RAC APPROVED RESEARCH PROJECTS

**PROJECT TITLE:** Genetic Mutations in Weill Marchesani Syndrome (WMS) in Saudi Arabia (RAC#2070008).

**INVESTIGATORS:** Al-Tassan N, Morales J, Bakheet D, Al-Mahrouqi R

**PROJECT DESCRIPTION:** The aim of the study is to identify families with WMS which is a rare connective tissue disorder associated with lens abnormalities, and screen for mutations in the common known genes (ADAMTS-10, FBN1).

**PROGRESS:** Sequencing of the whole coding region of the related genes (ADAMTS-10, FBN1) was completed in affected individuals from families with WMS phenotype. Novel mutations in ADAMTS10 and ADAMTS17 were identified. This project was completed and closed in 2014.

**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.

**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.

**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.

**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* and autosomal recessive variants.

**PROJECT TITLE:** Genetic Characterization of Hemoglobinopathies in Saudi Arabia (RAC#2080012).

**INVESTIGATORS:** Bakheet D, Al Jafreeri A, Warsy A, Al Anzi M, Al Tassan N

**PROJECT DESCRIPTION:** This study aims to identify and enroll patients with hemoglobinopathies (SCD,  $\alpha$ - and  $\beta$ - thalassaemia) to characterize mutations in  $\alpha$  and/or  $\beta$ - globin gene and also screen for genetic modifier genes in these patients that are associated with mild and severe disease and secondary conditions.

**PROGRESS:** 130  $\beta$ - thalassaemia patients were enrolled from KKHU and KFSHRC. Screening of the  $\beta$ - globin gene identified disease causing mutations and a large number of SNP variants some of these are novel. Haplotyping of these patients was generated using 7 RE. MLPA was used to identify large deletions in these patients. This project was completed and closed in 2014.

**PROJECT TITLE:** Identification of Sulfonylurea Receptor SUR1 and Potassium Inward Rectifying Receptor Kir6.2 Genes Mutations in Saudi Patients With Persistent Hyperinsulinemic Hypoglycemia of Infancy (Nesidioblastosis) (RAC#2020 007).

**INVESTIGATORS:** Bakheet D, Tassan N and Bin Abbas B

**PROJECT DESCRIPTION:** This study aims to diagnose patients with PPHI and enroll them to screen for mutations in SUR1/Kir6.2 receptors gene in the entire genomic sequence.

**PROGRESS:** 15 patients were enrolled from KKSH&RC Screening for both genes identified a number of novel and reported variants. Deletions were also identified in some patients. This project was completed and closed in 2014.

**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.

**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 digenic mutation was ascertained in zebra fish.

### 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.

**PROGRESS:** Screening for the reported genes was completed in ~94 AD, AR and /sporadic index cases. Variants were identified and are being assessed to determine frequencies in normal controls. Targeted sequencing using the SHGP neuro panel identified novel variants in 3 families. Exome sequencing of index cases is being performed in the Saudi Human Genome Program Lab.

**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

**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.

### SELECTED ACHIEVEMENTS FOR 2014

- 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.
- Balasubramaniana R, Choia j, Francescattob L, WillerbJ, Hortona E, Asimacopoulosc E, Stankovicc K, Plummera L, Bucka C, Quintond R, Nebesiof T, Mericqg V, Merino P, Meyer BF, Moniese D, Gusellai J, Tassan N, Katsanis N, and. Crowley WF. Functionally compromised CHD7 alleles in patients with Isolated GnRH Deficiency. *Proc Natl Acad Sci U S A*. 2014 Dec 16;111(50):17953-8.

- Ramzan K, Taibah K, Tahir Al, Al-Tassan N, Berhan A, Khater AM, Al-Hazzaa SA, Al-Owain M, Imtiaz F: ILDR1: Novel mutation and a rare cause of congenital deafness in the Saudi Arabian population. *Eur J Med Genet.* 2014,57(6):253-8.
- Muiya NP, Wakil S, Al-Najai M, Tahir Al, Baz B, Andres E, Al-Boudari O, Al-Tassan N, Al-Shahid M, Meyer BF, Dzimir N: A study of the role of GATA2 gene polymorphism in coronary artery disease risk traits. *Gene* 2014,10;544(2):152-8.

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## CARDIOVASCULAR AND PHARMACOGENOMICS

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The Cardiovascular and Pharmacogenomics Unit has until recently focused on understanding the role of gene polymorphism(s) (SNPs) in the manifestation of complex cardiovascular diseases, in particular coronary artery disease (CAD) and its risk traits, including diabetes, hypertension and dyslipidaemic disorders. In these studies, we employ a three-pronged approach of (a) linkage analysis using Affymetrix whole genome scan 250 styl array platform (b) genome-wide association study on Affymetrix axiom platform and (c) targeted population-based studies on individual genes using the Taqman assay on ABI real-time PCR system. To date, we have identified several chromosomal loci linked to early onset of CAD and dyslipidaemia through linkage analysis. This has led us to searching for potential target genes and gene variants, and the identification of several novel mutations in suspected genes. Furthermore, our ongoing analysis of our genome-wide association studies (GWAS) results in >6000 individual with CAD and its important risk traits, has also revealed several novel genes/gene variants linked particularly to hypertension, type 2 diabetes mellitus, obesity and dyslipidaemia in ethnic Arabs. This exciting data is being prepared for publication. As a spin-off idea, we embarked on examining more closely the non-coding entities/genomic regions as a primary cause of complex diseases. The synopsis of these results is discussed below under the respective projects. Besides, in this period we also worked on five projects with collaborators both at national and international levels.

Apart from the above-mentioned research activities, the Unit is also currently involved in the establishment of the Personalized Medicine Centre in line with the setting up of a regional PGENI program at KFSHRC.

**Nduna Dzimiri, PhD**  
HEAD

MEMBERS

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

## RESEARCH PROJECTS

**PROJECT TITLE:** Evaluation of the Relevance of Single Nucleotide Polymorphism for Coronary Artery Disease in the Saudi Population. RAC No. 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, using the ethnic Saudi Arab population as a study model. This is accomplished by employing both whole genome scanning approach using the Affymetrix 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, dyslipidaemia.

**PROGRESS:** In 2014, we focused primarily on analyzing our genome-wide association study (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 multiple CAD risk traits. Our studies also revealed that genetic changes in the untranslated regions, particularly the 3-UTR, of a great number of risk genes for CAD, an issue we are currently pursuing further in search for signalling mechanisms contributing to complex disease pathways.

**PROJECT TITLE:** Relevance of Lipid Metabolizing Proteins in the Treatment of Hypercholesterolemia and Coronary Heart Disease. RAC No.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 three Saudi families with heterozygous familial hypercholesterolemia (HFH) have yielded a wealth of information regarding possible loci linking early onset CAD with familial hypercholesterolaemia. Data on selected suspect genes point to multiple effects of some of the genes on several risk traits, which might explain some common pathways for these risk factors in triggering atherosclerosis.

**PROJECT TITLE:** Clinical and Molecular Characterization of Patients With Inherited Arrhythmogenic Disorders. RAC No. 2050035

**INVESTIGATORS:** Zohair Al-Hasnain, Nduna Dzimiri, Salma Majid, Majid Al-Fayyah, Yassn Al Manea, Mohammed Al-Owain and Brian Meyer

**PROJECT DESCRIPTION:** This study aims to identify genes linked to inherited arrhythmogenic disorders particularly the long QT syndrome (LQTS), Brugada and Sinus sick syndrome, in the Saudi population. This information should serve several clinical objectives including patient diagnosis stratification and prophylactical strategies in the management of arrhythmogenic disorders.

**PROGRESS:** More than 100 Saudi families with various forms of inherited arrhythmogenic disorders (IAD) have been recruited thus far. The maladies include Romano-Ward syndrome, Jervell and Lange-Nielsen, Brugada syndrome, sick sinus syndrome, arrhythmogenic right ventricular dysplasia and catecholaminegic polymorphic ventricular tachycardia. A high number of heterozygous mutations in KCNQ1 and PKP2, as well as homozygous mutations in KCNQ1, CASQ1 and SCN5A genes were found in several of the families. The data represents the largest cohort of

Arab patients and demonstrates the impact of high degree of consanguinity on causative genotypes for IAD.

**PROJECT TITLE:** Role of the Scaffold Protein Striatin in Regulating Cardiac Remodelling. RAC No. 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. In vascular endothelial cells, the protein assists in the assembly of membrane signalling complexes by anchoring to the oestrogen receptor and eventually modulating signal transduction. It also probably serves as a scaffold protein within a multicomplex network of kinases and phosphatases primarily consisting of Mob3, GCK, CCM and PP2A. The ultimate outcome of the signalling pathways regulated by these kinases and phosphatases suggest multifunctional roles for striatin within the cell (i.e. cell death, cell growth, proliferation, cell cycle). During cardiac development, the remodelling program is highly active in order to accommodate for the demand. 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 was reported in different tissues and cell lines, there is 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, reported 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 arrhythmogenic 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 are proposing to study 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 will be manipulating the levels of striatin by employing 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 demonstrated that striatin interacts with the calcium binding protein calmodulin in a calcium sensitive way in cardiac lysates. We also found that striatin complexes with SLMAP, a membrane protein involved in regulating the excitation-contraction module in the heart. Further preliminary studies indicate that striatin is associated with a network of proteins (~35 potential targets) in the heart, a notion we are currently chasing.

**PROJECT TITLE:** The role of Gene Polymorphism in the Regulation of the Thyroid Stimulating Hormone Level. RAC No. 2100025.

**INVESTIGATORS:** Nduna Dzimiri, Ali Alzahrani, Maha Alrasheed, Abdulraof Ahmad Al Mahfouz, Abdullah Hamad Al Khenizan, Jalal Jalaluddin Bhuiyan

**PROJECT DESCRIPTION:** Circulating thyroid hormone levels are tightly regulated by a feedback control system

in which changes in the serum thyroid hormone levels induce inverse changes in the TSH serum levels. Recent studies have shown an association between the risk of differentiated thyroid cancer (DTC) and the high TSH level within normal range. In the present study, we hypothesize a relationship between TSH levels and the presence of genetic variations in its synthesis, metabolism, transport or in thyroid hormone action(s). In this study, we test this notion by evaluating the relationships of TSH, thyroid hormone levels and polymorphisms in thyroid stimulating hormone, beta (TSHB), iodothyronine deiodinase types I, II, III (DIO1, DIO2, DIO3), sodium/iodine symporter (NIS), and paired box gene 8 (PAX8) in subjects with no evidence of thyroid disease. A clear correlation between high normal TSH and gene variants would be indicative of the potential of such genetic change(s) serving as marker(s) for increased predisposition to differentiated thyroid cancer (DTC). Accordingly, we would then compare the incidence of the discovered polymorphism(s) in patients with that in age- and sex-matched healthy individuals in a case control study setup. Ultimately, we hope to demonstrate that high normal TSH level is related to the presence of gene polymorphism(s) which not only predict(s) TSH levels, but also serve as a genetic marker for the high normal TSH-associated risk of DTC.

**PROGRESS:** To date, a number of variants and haplotypes in three of the six studied genes (NIS, TSHB and PAX8) have been associated with thyroid cancer, while some in the NIS and TSH have also been linked to differential response to thyroid hormone treatment.

## PUBLICATIONS

### ORIGINAL PEER-REVIEWED FULL-LENGTH PUBLICATIONS

- Wakil SM, Muiya NP, Tahir AI, Al-Najai M, Baz B, Andres E, Mazher N, Al-Tassan N, Alshahid M, Meyer BF, Dzimiri N. A new susceptibility locus for myocardial infarction, type 2 diabetes

mellitus and dyslipidaemia on chromosome 12q24. *Dis Markers*, 2014: 2014:291419. doi: 10.1155/2014/291419. Epub Jun 26, 2014

- Muiya NP, Wakil S, Al-Najai M, Tahir AI, Baz B, Andres E, Al-Boudari O, Al-Tassan N, Al-Shahid M, Meyer BF, Dzimiri N. A study of the role of GATA2 gene polymorphism in coronary artery disease traits. *Gene*, 544(2): 152-158, 2014.

### ABSTRACTS AND SCIENTIFIC CONFERENCE PROCEEDINGS

- Wakil SM, Muiya NP, Andres E, Baz B, Morahan G, Dzimiri N. DMET array identified unique changes in metabolic gene variants in ethnic Arabs. American Society of Human Genetics, San Diego, October 18–22, 2014.
- Nader M, Khalil B, Hoilat J, Algohie A, Bakheet D, Dzimiri N. Striatin is cleaved during apoptosis in a caspase-3 related manner: a step towards novel biomarkers for apoptosis. World Congress of Pharmacology, Cape Town, South Africa, July 13–18, 2014.
- Al-Rasheed MM, Alzahrani AS, Macadam A, Overall A, Gard P, Dzimiri N. The potential role of the sodium symporter gene polymorphism in the development of differentiated thyroid cancer. World Congress of Pharmacology, Cape Town, South Africa, July 13–18, 2014.
- Tayeb HT, Bakheet DH, Aijlan A, Jedai A, Zaza K, Dzimiri N. Genotyping of CYP2C19 Polymorphisms and its potential clinical application in the Saudi population. World Congress of Pharmacology 2014, Cape Town, South Africa, July 13–18, 2014
- Muiya NP, Wakil SM, Nguyen C, Andres E, Baz B, Morahan G, Meyer BF, Dzimiri N, Determination of PGENI gene variants by DMET chip in the Saudi population. World Congress of Pharmacology 2014, Cape Town, South Africa, July 13–18, 2014.
- Dzimiri N, Wakil SM, Nguyen C, Muiya P, Andres E, Baz B, Morahan G, Meyer BF. Genotyping of PGENI-related gene variants by genome-wide single nucleotide polymorphism analysis. World Congress of Pharmacology, Cape Town, South Africa, July 13–18, 2014

- Al-Samhari M, Al-Rasheed N, Al-Rejaie S, Ahmed R, Dzimir N. Possible Involvement of Janus Kinase-Signal Transducers and Activators of Transcription (JAK/STAT) Signaling Pathway in N-Acetylcysteine-Mediated Anti-depressant-Like Effects in a Rat Depression Model, Royal College of Psychiatrists International Congress, London, UK, June 24–27, 2014
- Nader M, Khalil B, Kvietys P, Bakheet D, Dzimir N. Striatin: a novel regulator of cardiomyocyte calcium homeostasis and contraction Experimental Biology, Boston, San Diego. April 26–30, 2014



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## COGNITIVE GENETICS RESEARCH UNIT

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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.

**Namik Kaya MSc, PhD**

HEAD

MEMBERS

**Mazhor Salem AlDosary MSc, PhD**

**AlBandary AlBakheet, MSc**  
(Currently Pursuing PhD)

**Maysoon Alsagob, MSc**  
(Grant Employee)

**Faten Almutairi**  
(Grant Employee)

**Rawan Almas**  
(Grant Employee)

## 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. Identification of Genes/Mutations Involving Neurologic Disorders (RAC# 2120022).
2. Molecular Studies on Mitochondrial Diseases in Saudi Arabia (KACST#11-BIO2221-20).
3. The Saudi-Arab diseaseome -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).
4. Positional Cloning of Genes Underlying Genetic Disorders with Prominent Neurodevelopmental Manifestations in Several Extended Families (RAC# 2060 035).
5. Molecular Genetic Studies in Chromosome Disorders (RAC# 2040 042).
6. Genetic Basis of Mental Retardation in Families from KSA (RAC# 2080-036).

## PUBLICATIONS

### PEER REVIEWED JOURNAL ARTICLES

- 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, Almutashri 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, Julaiify 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.
- Faqeih EA, Al-Owain M, Colak D, Kenana R, Al-Yafee Y, Al-Saman A, Albalawi F, Al-Sarar D, Domiaty D, Al-Dosary M, Daghestani M, Kaya N. Novel homozygous DEAF1 mutation leads to microcephaly and white matter disease. *Am J Med Genet A.* 2014 Jun;164(6):1565-70. doi: 10.1002/ajmg.a.36482. Epub 2014 Mar 25. PubMed PMID: 24668509.
- 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.
- Reiff RE, Ali BR, Baron B, Yu TW, Ben-Salem S, Coulter ME, Schubert CR, Hill RS, Akawi NA, Al-Younes B, Kaya N, Evrony GD, Al-Saffar M, Felie JM, Partlow JN, Sunu CM, Schembri-Wismayer P, Alkuraya FS, Meyer BF, Walsh CA, Al-Gazali L, Mochida GH. METTL23, a transcriptional partner of GABPA, is essential for human cognition. *Hum Mol Genet.* 2014 Feb 19. [Epub ahead of print] PMID:24501276 [PubMed - as supplied by publisher].



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## DEVELOPMENTAL GENETICS

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The Section of Developmental Genetics studies the developmental role of genes as inferred from their involvement in various birth defects.

**Fowzan Alkuraya, PhD**  
HEAD

MEMBERS

Agaadir Almoisheer  
Anas Alazami  
Fatma Alzahrani  
Ferdous Abdulwahab  
Hadeel Alsharif  
Hanan Shamseldin  
Mais Omar Hashem  
Mohammed Aldahmesh  
Niema Ibrahim  
Nisha Patel  
Rana Alomar  
Ranad Shaheen  
Sara Alqattan  
Shamsa Saleh  
Tarfa Alshidi

## SELECTED ACHIEVEMENTS FOR 2014

The year 2014 marks an important milestone when our section identified the 100<sup>th</sup> novel disease gene. Our list of publications speaks for the achievements of the unit for the year 2014.

## RESEARCH PUBLICATIONS

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## FIRST ARABIAN HEREDITARY DEAFNESS (FAHD)

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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 & PSCDR 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), and Familial Pulmonary Fibrosis (RAC# 2120 009) 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 1000 patients and their families with over 120 different genetic diseases now available at KFSH&RC. In particular, 55 of these genetic tests are designed to molecularly characterize inherited errors of metabolism. In 2014, under the supervision of Dr. Faiqa Imtiaz, the Molecular Diagnostic Laboratory (MDL) successfully performed and reported 255 prenatal molecular diagnostic tests for 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.

**Faiqa Imtiaz Ahmad, PhD**  
HEAD

MEMBERS

**Khushnooda Ramzan, PhD**  
**Rabab Allam, MSc**  
**Lolwa Gomaa**  
**Sultan Al-Amer, MSc**

## RESEARCH PROJECTS

**PROJECT TITLE:** Molecular Characterization of Hereditary Deafness in Saudi Population (RAC# 2100 001 & PSCDR 2015).

**INVESTIGATORS:** Dr Faiqa Imtiaz (PhD), Dr Mohammad Al-Owain (MD), Dr Khushnooda Ramzan (PhD), Dr 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 (PSCDR 2015). 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:** Clinical and Molecular Basis of Laron Syndrome Patients in Saudi Arabia (RAC# 2101 034):

**INVESTIGATORS:** Dr Abdullah Al-Ashwal (MD), Dr Faiqa Imtiaz (PhD), Dr 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:** Dr. Eid Al-Mutairy (MD), Dr Faiqa Imtiaz (PhD), Dr 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.

## PUBLICATIONS

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## GENE THERAPY UNIT

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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 oncogenic  $Braf^{V600E}$  would go through OIS via p53 dependant mechanism. These data reinforce the importance of rigorous control of serum TSH in PTC patients.

**Yufei Shi, PhD**  
HEAD

MEMBERS

**Minjing Zou**  
**Essa Baitei**  
**Roua Al-Rijjal**  
**Huda Bin Essa**

## RESEARCH PROJECTS

**PROJECT TITLE:** IL-12 Gene Therapy of Thyroid Cancer in BRAF<sup>V600E</sup> 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<sup>V600E</sup> mutations are frequently identified in more than 40% PTC. Although most differentiated thyroid carcinomas can be cured by surgery and <sup>131</sup>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 BRAFV600Emutation 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- $\beta$  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. A manuscript has been submitted for publication.

**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<sup>V600E</sup> 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<sup>V600E</sup> 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<sup>G12D</sup> and Spry1 knockout, and the other with concomitant thyroid specific expression of BraF<sup>V600E</sup> and Spry1 knockout.

**PROGRESS:** Kras<sup>G12D</sup> causes lung cancer rapidly, but is not sufficient to induce thyroid cancer. TPO-Kras<sup>G12D</sup> and TPO-BraF<sup>V600E</sup> strains were created, which allow conditional expression of Kras<sup>G12D</sup> or BraF<sup>V600E</sup> 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<sup>G12D</sup> and TPO-Kras<sup>WT</sup> mice. In contrast, only mild thyroid enlargement and hyperplasia were observed in TPO- Kras<sup>G12D</sup> mice without treatment. Distinct thyroid histology was found between TPO- Kras<sup>G12D</sup> and TPO-Kras<sup>WT</sup> mice: thyroid from TPO-Kras<sup>G12D</sup> showed follicular hyperplasia whereas in TPO-Kras<sup>WT</sup> this structure was replaced by papillary hyperplasia. Among 10 TPO- Kras<sup>G12D</sup> 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<sup>G12D</sup> mediated oncogenesis, leading to FTC. SPRY1 may function as a molecular switch to control MAPK signaling and its down-regulation by BraF<sup>V600E</sup> favors PTC development. A manuscript has been submitted for publication.

**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, BRAFV600E is the most common mutation (44%) and has been associated with poorer prognosis and more aggressive clinical outcome. BRAFV600E 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 BraFV600E-induced

PTC (BVE–PTC) requires constant TSH stimulation. BraF<sup>V600E</sup>-induced senescence occurs in human and mouse naevi, protecting melanocytes against BraF<sup>V600E</sup>-driven proliferation and progression into melanoma. This process has not been demonstrated in mouse models of BraF<sup>V600E</sup>-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<sup>WT</sup> mice. Regression of the transplanted tumors was observed in both nude and TPO–BraF<sup>WT</sup> 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<sup>V600E</sup> 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<sup>V600E</sup> 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. A manuscript has been submitted for publication.

**PROJECT TITLE:** Expression of CYP24A1, the Catabolizing Enzyme of Vitamin D, in Thyroid Tumor Development and Progression (RAC# 2111 101).

**INVESTIGATORS:** Minjing Zou, and Yufei Shi

Project description: Vitamin D exists in two major forms: ergocalciferol (vitamin D<sub>2</sub>), and cholecalciferol (vitamin D<sub>3</sub>). Both forms need two-step hydroxylation at carbons 1 and 25 for activation. 1 $\alpha$ , 25(OH)<sub>2</sub>D<sub>3</sub> (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 1 $\alpha$ , 25(OH)<sub>2</sub>D into inactive 1 $\alpha$ , 24,25(OH)<sub>3</sub>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 1 $\alpha$ , 25(OH)<sub>2</sub>D<sub>3</sub>. 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<sup>V600E</sup> mutation was detected by PCR-DNA sequencing analysis. The interaction between BRAFV600E 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<sup>V600E</sup> mutation ( $p < 0.01$ ). In thyroid cancer cell lines expressing BRAF<sup>V600E</sup>, CYP24A1 expression was significantly higher when compared to those without BRAF<sup>V600E</sup> expression. BRAF<sup>V600E</sup> transgene expression in CAL62 cell line can induce CYP24A1 expression. Furthermore, BRAF<sup>V600E</sup> 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<sup>V600E</sup> 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<sup>V600E</sup> inhibitor PLX4720.

## PUBLICATIONS

- Increased CYP24A1 expression is associated with BRAF<sup>V600E</sup> mutation and advanced stages in papillary thyroid carcinoma. Zou MJ, BinHumaid FS, Al-zahrani AS, Baitei EY, Al-Mohanna FA, Meyer B, and Shi Y. *Clin Endocrinol*, 81:109-16, 2014.
- Concomitant Mutations in RAS, RET/PTC, or BRAF in Advanced Stage of Papillary Thyroid Carcinoma. Zou MJ, Baitei EY, Al-zahrani AS, BinHumaid FS, Al-Rijjal RA, Meyer B, and Shi Y. *Thyroid*, 24:1256-66, 2014.
- Hypophosphatemic Rickets Caused by a Novel Splice Donor Site Mutation and Activation of Two Cryptic Splice Donor Sites in the PHEX Gene. Zou MJ, Buluş D, Al-Rijjal RA, Andiran N, BinEssa H, Kattan WE, Meyer B, and Shi Y. *J Pediatr Endocrinol Metab*.28:211-216, 2014.

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## GENOTYPING CORE FACILITY

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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.

**Salma Wakil, PhD**  
HEAD

MEMBERS

**Haya Al Dusery, BSc**  
**Samiya Hagos, BSc**  
**Rula Abothuraya, BSc**

**Batool Baz, Msc**  
(on study leave)

## LIST OF RAC APPROVED RESEARCH PROJECTS

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

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.

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:**

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 sub-types 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):**

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 population<sup>7</sup>. 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 Rheumatoid Arthritis.**

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.**

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.**

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.**

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**

- 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.* 2014 Dec 11.
- Mutation of LACC1 is associated 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.* 2014 Sep 12.
- A new susceptibility locus for myocardial infarction, hypertension, type 2 diabetes mellitus, and dyslipidemia on chromosome 12q24. Wakil SM, Muiya NP, Tahir AI, Al-Najai M, Baz B, Andres E, Mazhar N, Al Tassan N, Alshahid M, Meyer BF, Dzimir N. *Dis Markers.* Epub 2014 Jun 26.
- 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.
- Novel B4GALNT1 mutations in a complicated form of Hereditary Spastic Paraplegia. Salma M Wakil, Dorota M Monies, Khushnooda Ramzan, Samya Hagos, Laila Bastaki, Brian F. Meyer and Saeed Bohlega. *Clinical Genetics* 2014 Nov;86(5):500-501.
- Infantile Ascending Spastic Paralysis caused by a novel ALS2 mutation identified by Homozygosity Mapping. Salma M Wakil, Rula Abuthuraya, Khushnooda Ramzan, Samya Hagos, Haya Al Dossari, Rana Al Omar, Hatem Murad, Aziza Chedrawi, Zuhair N Al-Hassnan, J Finsterer and Saeed Bohlega. *Gene.* 2014 Feb 15;536(1):217-220.



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## IMMUNOGENETICS

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The ImmunoGenetics section activity is concentrated on the genetic causes of immunodeficiency in Saudi Arabia and on the chromatin and transcriptional regulation of genes that regulate the immune system function and development. Disregulation of any of the immune system genes can lead to many debilitating diseases such as immune deficiencies, cancer and auto-immunity. In addition, our section is studying the regulation of the T-Cell receptor alpha and delta (TCRa/d) gene locus and on the role of ROR $\gamma$ T transcription factor in controlling T cell development and its role in protecting us from developing auto-immune diseases and cancer. New findings are described below.

**Abbas Hawwari, PhD**  
HEAD

MEMBERS

**Safa Al-Hissi**  
**Lina El Baik**  
**Noukha Nader**  
**Atia Sheereen**  
**Tanzeel Al Ameen**  
**Amal Jabr**  
**Al-Shaimmaa Al-Hallaj**

## LIST OF RAC-APPROVED RESEARCH ACTIVITY

**PROJECT TITLE:** Underlying Genetics of Familial Hemophagocytic Lymphohistiocytosis (FLH) in Saudi Arabia. RAC No. 2080 041.

**INVESTIGATORS:** Dr. Atia Sheereen, Dr. Ali Al-Ahmari, Tanzeel Al Ameen, Lina El Baik, Amal Jabr, Dr. Bandar Al Saud, Dr. Ibrahim Al-Fawaz, Dr. Mohab Ayas, and Dr. Abbas Hawwari

**PROJECT DESCRIPTION AND PROGRESS:** Hemphagocytic lymphohistiocytosis (HLH) is a serious immune disorder characterized by a severe hyperinflammation on top of various inherited or acquired immunodeficiencies. The hallmark of the disease is an impaired or absent function of natural killer (NK) cells and cytotoxic T cells (CTL). Familial Hemophagocytic Lymphohistiocytosis (FHL) is an autosomal recessive condition in which several genetic defects have been identified. Genes that have been described in the literature to associate with FHL are PRF1, UNC13D, STX11, and STXBP2. A total of 88 patients diagnosed with FLH at our institute were recruited and their DNA was sequenced of all exons and their flanking intronic region for all the implicated genes. Forty-three patients were identified with homozygous mutations. 6 mutations (one novel) from 10 patients and 3 novel mutations from 7 patients were found in PRF1 or UNC13D respectively. Only one novel missense mutation was found in 9 patients in the STX11 gene. Similarly, only one novel missense mutation was found in 16 patients in STXBP2 gene. An additional patient was found to have compound heterozygosity; one being a missense and the other one being a splice site mutations in STXBP2 gene. The remaining 45 negative patients were screened for mutations in other genes that have implicated in other immunodeficiencies that have similar aspects to FHL such as RAB27A, XIAP, and LYST. No mutations were found in RAB27A gene. However, 2 splice sites and one missense mutations were found in three patients in the LYST gene and one patient was found to have a novel

insertion of one nucleotide in the XIAP gene leading to a stop codon further downstream. In conclusion, the known genes associated with FHL disease can only explain forty seven patients (53.4%). We were not able to identify any genetic changes in any of the known gene in 41 patients (46.6%). We are currently performing whole exome sequencing on DNA from representative patients to identify novel genes.

**PROJECT TITLE:** Underlying Molecular Genetic Defects of Primary Immunodeficiency Diseases in Saudi Arabia. RAC No. 2080 025.

**INVESTIGATORS:** Dr. Hamoud Al-Mousa, Safa Al-Hissi, Lina El Baik, Al-Shaimmaa Al-Hallaj, Esteban Borrero, Asma Abustaiteh, Dr. Abdulaziz Al-Ghonaum, Dr. Hasan Al-Dhekri, Dr. Saleh Al-Muhsen, Dr. Rand Arnaout, Dr. Bandar Al-Saud and Dr. Abbas Hawwari

**PROJECT DESCRIPTION AND PROGRESS:** There are wide varieties of primary immunodeficiency diseases (PIDs) that are caused by congenital defects of the immune system. Today, 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 enabled 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 overall rates due to high rate of consanguinity, and there is a need to delineate the molecular bases underlying them. Based on our experience as we have identified a substantial number of novel mutations, it is anticipated that novel loci/genes that are unique to the Saudi population will be discovered. Results roots out from these studies will benefit patients and their families in terms of counseling, disease prevention through pre-implantation genetic diagnosis and prenatal diagnosis.

**The following have been submitted for publications.**

#### **Premature birth in reticular dysgenesis indicates a role of AK2 in growth and development**

**Hamoud Al-Mousa, Safa Al-Hissi, Namik Kaya, Abbas Hawwari**

Reticular dysgenesis is the most severe form of inborn SCID. It is characterized by absence of granulocytes and almost complete deficiency of lymphocytes in peripheral blood, hypoplasia of the thymus and secondary lymphoid organs, and lack of innate and adaptive humoral and cellular immune functions, leading to fatal septicemia within days after birth. In addition, affected newborns have bilateral sensorineural deafness. The gene encoding the mitochondrial energy metabolism enzyme adenylate kinase 2 (AK2) is mutated in individuals with reticular dysgenesis. Allogeneic hematopoietic stem cell transplantation (HSCT) can correct hematopoiesis. We aimed to review clinical, immunological, molecular genetic defect and outcome of stem cell transplantation of confirmed AK2 deficiency. Retrospective review of clinical, immunological and outcome of hematopoietic stem cell transplantation of all cases suspected to have reticular dysgenesis. Identified cases were screened for mutations in AK2 gene. Two patients from two unrelated families were identified, presented with early onset of recurrent infections, chronic diarrhea and severe neutropenia unresponsive to GCSF therapy. Immunological work up showed

panhypogammaglobulinemia, T-B-NK- SCID phenotype and both had severe poor lymphocytes proliferation in response to mitogen stimulation. Bone marrow aspiration revealed evidence of absent granulopoiesis. They had abnormal brain stem-evoked response audiometry tests, compatible with bilateral sensorineural deafness. Both found to have a novel mutation on AK2 gene (R157P). They underwent successful hematopoietic stem cell transplantation from a genoidentical donor and from unrelated matched umbilical cord resulting into correction of hematopoiesis and immune reconstitution. Novel hypomorphic AK2 mutation were identified in both unrelated patients expected to impair protein function. Hematopoietic stem cell transplantation from related and unrelated umbilical cord using full myeloablative conditioning can correct the hematopoiesis and immune defects.

#### **Novel ZAP70 mutations causing Severe Combined Immunodeficiency Disease in Saudi Arabia**

**Hamoud Al-Mousa, Safa Al-Hissi, Osama Alsmadi, Hasan Al-Dhekri, Abdulaziz Al-Ghoniaum, Saleh Al-Muhsen, Bandar Al-Saud, Rand Arnaout, and Abbas Hawwari.**

SCID with selective CD8 deficiency is a very rare type of SCID typically caused by defects in ZAP70 ( $\zeta$ -chain-associated protein kinase of 70 kDa) gene. We aimed to present the clinical and molecular genetic defects of three cases of ZAP70 deficiency in Saudi Patients. Three patients diagnosed with SCID and selective CD8 deficiencies were screened for mutations in ZAP70 gene. All patients were presented with the typical clinical manifestations including chronic diarrhea, failure to thrive, severe opportunistic infections, CD8 lymphopenia, hypogammaglobulinemia, and poor lymphocyte response to mitogen stimulation. Two novel missense mutations (G536S, and R190T) in ZAP70 gene were identified in three patients from three families. Parents of some patients were confirmed as carriers (heterozygous) of the respective mutation. No similar mutations were found among 96 DNA samples derived from normal Saudi blood donors. All three

patients had missense mutations in the ZAP70 gene, expected to result into impaired protein function. Although all mutations were missense, the clinical phenotypes of our patients were severe with early presentations, indicating a straight forward genotype-phenotype correlation.

### Clinical, Immunological, and Molecular Characterization of Janus Kinase 3 Deficiency Causing Severe Combined Immunodeficiency Disease in Saudi Arabia.

H. Al-Shammari, S. Al-Hissi, O. Al-Smadi, H. Al-Dhekri, A. Al-Ghoniaum, S. Al-Muhsen, B. Al-Saud, R. Arnaout, H. Al-Mousa and A. Hawwari.

Molecular defects in IL2Rg gene are the most common genetic cause of T-B+NK- SCID worldwide followed by Janus Kinase 3 (JAK3). However, no report has been published to describe the genetic defects of T-B+NK- SCID in Saudi Arabia. Due to high consanguinity rate in Saudi society, most cases that we observe in our patient population are mainly due to autosomal recessive pattern of inheritance. Hence, patients with T-B+NK- SCID were screened for mutations in JAK3 gene. Eight patients from 5 families diagnosed with T-B+NK- were screened for mutations in JAK3 gene. The diagnosis of T-B+NK- SCID is based on the profound, characteristic lymphopenia and early clinical presentation of immunodeficiency often with strong family history indicating an autosomal recessive inheritance. Five novel homozygous JAK3 mutations were identified. Three closely related patients (two siblings and a cousin) carry the nonsense mutation (Q305X) ; one patient was found to have a deletion mutation (A3381fsX14) leading to a stop codon 14 amino acid downstream; and two brother patients carry the R403C missense mutation. The remaining two patients carry either E1019K or R103H missense mutations. Contrary to the available data of X-linked IL-2 common gamma chain gene defect of T-B+NK- SCID as the most common, we demonstrate here that in the Kingdom of Saudi Arabia, the most common form of T-B+NK- SCID is the autosomal

recessive mode of inheritance associated with JAK3 deficiency.

### Genetic defects of Griscelli syndrome type 2 in Saudi Arabia.

Hamoud Al-Mousa, Safa Al-Hissi, Abdulaziz Al-Ghoniaum, Hasan Al-Dhekri, Saleh Al-Muhsen, Bandar Al-Saud, Rand Arnaout, and Abbas Hawwari.

Griscelli syndrome type 2 is a rare autosomal recessive disorder that results in characteristic pigmentary dilution of the skin and the hair associated with an immune defect, leading to episodes of a life-threatening uncontrolled T lymphocyte and macrophage activation syndrome known as accelerated phase or hemophagocytic lymphohistiocytosis (HLH). We aimed to present the clinical and underlying genetic defects of eleven Saudi patients. Griscelli syndrome type 2 was diagnosed based on characteristic irregular large melanin clumps in hair shafts viewed by light microscopy, the hypopigmented skin and HLH picture. All patients were screened for mutations in RAB27A gene. Six mutations were identified in eleven patients screened from nine families. Four were novel mutations (W73X, A92fsX7, K134Q, and Q172X) identified in four patients from four families. Two known mutations causing disease (R200X and R50fsX33) were identified in seven patients from five families. Parents of all patients were confirmed as carriers of the respective mutation. No similar mutations were found among 96 DNA samples derived from normal Saudi blood donors. Rab27A gene defects are responsible for all Griscelli syndrome type 2 in Saudi Arabia. Novel and known mutations were identified that expected to result into impaired protein function with severe clinical phenotype.

**PROJECT TITLE:** Transcriptional Regulation of TCR $\alpha$ /d Locus. RAC No. 2080 019.

**INVESTIGATORS:** Dr. Abbas Hawwari, Dr. Goran Matic, Dr. Edward Hiiti

**PROJECT DESCRIPTION AND PROGRESS:** Humeral immunity depends on the generation of diverse repertoire of immunoglobulin (Ig) and T-cell receptor (TCR). For this to happen, mature Ig and TCR genes are generated by the rearrangement of one of each of the Variable (V), Diversity (D), and Joining (J) gene segments by the process of V(D)J recombination. Each gene segment is flanked by Recognition Signal Sequences (RSS). This process occurs during lymphocyte development, as well as in response to exogenous stimuli and it is tightly controlled, so that it is restricted to the appropriate cell lineage and stage of development. Recombination is initiated by DNA breaks mediated by Rag1 and Rag2 proteins at two RSS borders which the normal rejoining process resolves both sets of DNA ends efficiently. Failure of the normal rejoining triggers cellular DNA damage sensors leading to cell death and the prevention of oncogenic transformation. Impairment of these responses may allow alternative DNA repair pathways to mediate rejoining of antigen receptor genes with sites elsewhere in the genome. This breach on DNA integrity may lead to lymphoma-associated chromosomal translocations, which is a central feature of neoplasms in the immune system such as non-Hodgkin's lymphoma (NHL) and acute leukemia. So, it is critically important to understand the normal regulation of V(D)J recombination at the molecular level in order to understand the safe mechanism employed by cells to prevent translocation and hence preventing transformation. It became very clear in the last few years that V(D)J recombination is regulated at the level of gene transcription and chromatin structure. To do that we have been characterizing five promoter elements that associate with different gene segments and dictate at what stage of T cell development these segments are activated. For examples, TRADV15-1 gene segment in the TCR $\alpha$ /d locus is active in double negative (DN) stage of T cell development only which results in the rearrangements of this gene segments to generate TCR $\delta$  protein in only DN thymocytes. On the other hand the TRAV12-2 gene segment is active in double positive (DP)

thymocytes only and rearranges to generate TCR $\alpha$  protein in only DP thymocytes. To study the mechanism by which these two promoters exert their tissue and temporal specificity, we generated a knock-in mouse that has the TRAV12-2 promoter replaced with the TRADV15-1 promoter. In addition, we have bred this mouse onto the Rag deficient background with or without TCR $\beta$  transgene. We are currently analyzing the changes of the TRAV12-2 gene segment tissue and temporal specificity as well as changes in chromatin and transcriptional activity of the knocked-in promoter.

**PROJECT TITLE:** ROR $\gamma$ t Role in T-Cell Development, Autoimmunity and Transformation. RAC No. 2080 046.

**Investigators:** Dr. Abbas Hawwari, Ms. Asma Abustaiteh, Dr. Namik Kaya, Dr. Dilek Colak, Dr. Goran Matic.

**PROJECT DESCRIPTION AND PROGRESS:** ROR $\gamma$ t, a member of the hormone nuclear receptor super family, is a transcription factor that activates or suppresses many genes. The function of ROR $\gamma$ t was studied in multiple mouse models that are deficient in ROR $\gamma$ t. ROR $\gamma$ -/- mice lack both ROR $\gamma$ t and ROR $\gamma$  (an isoform variant of ROR $\gamma$ t) and ROR $\gamma$ <sup>GFP/GFP</sup> mice (do not express ROR $\gamma$ t but express EGFP instead). These mouse models showed that ROR $\gamma$ t 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. ROR $\gamma$ t was shown to be indispensable for the development of secondary immune organs such as Peyer's patches (Pp), and lymph nodes (LN). Other defects due to ROR $\gamma$  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, ROR $\gamma$ t is involved in the development of autoimmune diseases and thymic lymphoma. Our knowledge of the molecular mechanism by which ROR $\gamma$ t controls the development of immune

cells, organs and structures and protect against autoimmunity and thymic lymphoma is lacking. We think that in order to understand these processes, we need to understand: first, what controls ROR $\gamma$ t expression and why it is restricted to only small numbers of immune cell types, second, the genes that are regulated by ROR $\gamma$ t and third, what proteins interact with ROR $\gamma$ t to facilitate its function. This knowledge will help us understand, not only the development of DP thymocytes, LN, Pp, CP, ILF, and Th17, but also the process by which ROR $\gamma$ t

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 a similar fashion to the success story with estrogen receptor and breast cancer. We have are currently doing Chlp-Seq two-hybrid screen experiments on DP, ISP, Th17 and Intestinal T cells. Additionally, we are looking at whole genome expression analysis of the same cell types between WT and ROR $\gamma$  deficient mice. Results will be forthcoming.

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## NEWBORN SCREENING & BIOCHEMICAL GENETICS LAB

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The Newborn Screening & Biochemical Genetics Lab (NSBGL) at KFSH&RC provides clinical (newborn) screening services as well as diagnostic biochemical genetic studies which are used by patients within KFSH&RC as well as outside KFSH&RC (throughout KSA). Our newborn screening service continues to grow steadily.

**Majed Dasouki, PhD**  
DIRECTOR

### MEMBERS

**Majed Dasouki, MD**

**Ali Al Odaib, PhD**  
[KSCDR & NSBGL]

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**Minnie Jacob**

**Mahdi Ameen Alali**

**Ali Alnakhli**

**Ebtisam Al-Humaidi**

**Eklass Quraann**

### LIST OF RAC APPROVED RESEARCH PROJECTS

1. Genetics of Aplastic Anemia in Saudi Arabia. [KACST project (13-BIO1978-20)].
2. Development of Population-Based Newborn Screening for primary Immunodeficiency Diseases in Saudi Arabia. [KACST project (13-BIO755-20)].

### SELECTED ACHIEVEMENTS FOR 2014:

1. In 2014, NSBGL ran 61,365 newborn screening tests as well as 8600 diagnostic metabolic tests.
2. NSBGL continues to increase the number of newborn screening samples being referred through the enrollment of additional hospitals. Our current newborn screening load is estimated at 68,000 cases/year.
3. In Spetmber, 2014, Dr. Anas AbdelRahman, an analytical chemist with expertise in metabolomics, joined our lab as an associate scientist.

### RESEARCH PUBLICATIONS

- Kala Ahluwalia G, Dasouki M, Lennon A. Phenotypic variation of autosomal recessive pseudohypoaldosteronism type I: a case in point. *Clin Case Rep*. 2014 Dec;2(6):326-30. Epub 2014 Sep 15.
- Dasouki M, Saadi I, Ahmed SO. THPO-MPL pathway and bone marrow failure. *Hematol Oncol Stem Cell Ther*. 2014 Nov 29. pii: S1658-3876(14)00107-1. [Epub ahead of print]
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- Bushby K, Finkel R, Wong B, Barohn R, Campbell C, Comi GP, Connolly AM, Day JW, Flanigan KM, Goemans N, Jones KJ, Mercuri E, Quinlivan R, Renfroe JB, Russman B, Ryan MM, Tulinius M, Voit T, Moore SA, Lee Sweeney H, Abresch RT, Coleman KL, Eagle M, Florence J, Gappmaier E, Glanzman AM, Henricson E, Barth J, Elfring GL, Reha A, Spiegel RJ, O'donnell MW, Peltz SW, Mcdonald CM; PTC124-GD-007-DMD STUDY GROUP. Ataluren treatment of patients with nonsense mutation dystrophinopathy. *Muscle Nerve*. 2014 Oct;50(4):477-87.
- Dasouki M, Jawdat O, Almadhoun O, Pasnoor M, McVey AL, Abuzinadah A, Herbelin L, Barohn RJ, Dimachkie MM. Pompe disease: literature review and case series. *Neurol Clin*. 2014 Aug;32(3):751-76.
- Roberts JL, Gandomi SK, Parra M, Lu I, Gau CL, Dasouki M, Butler MG. Clinical report of a 17q12 microdeletion with additionally unreported clinical features. *Case Rep Genet*. 2014;2014:264947. Epub 2014 Jun 2.
- Usrey KM, Williams CA, Dasouki M, Fairbrother LC, Butler MG. Congenital Arthrogryposis: An Extension of the 15q11.2 BP1-BP2 Microdeletion Syndrome? *Case Rep Genet*. 2014;2014:127258. Epub 2014 Feb 12.
- Dasouki M, Roberts J, Santiago A, Saadi I, Hovanes K. Confirmation and further delineation of the 3q26.33-3q27.2 microdeletion syndrome. *Eur J Med Genet*. 2014 Feb;57(2-3):76-80. doi: Epub 2014 Jan 22.
- Janssen E, Tsitsikov E, Al-Herz W, Lefranc G, Megarbane A, Dasouki M, Bonilla FA, Chatila T, Schneider L, Geha RS. Flow cytometry biomarkers distinguish DOCK8 deficiency from severe atopic dermatitis. *Clin Immunol*. 2014 Feb;150(2):220-4. Epub 2013 Dec 31.
- Roberts JL, Hovanes K, Dasouki M, Manzardo AM, Butler MG. Chromosomal microarray analysis of consecutive individuals with autism spectrum disorders or learning disability presenting for genetic services. *Gene*. 2014 Feb 1;535(1):70-8. Epub 2013 Nov 2.
- Faiyaz-Ul-Haque MI, 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 l2-hydroxyglutaric aciduria in Arab kindreds. *Ann Saudi Med*. 2014 Mar-Apr;34(2):107-14.

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## SEQUENCING CORE FACILITY

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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.

**Dorota Monies, PhD**

HEAD

MEMBERS

**Muna Al Breacan, BSc**

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**Sara Al Haibey, BSc**

**Dyala Jaroudi, MSc**

**Ewa Naim, MPharm**

## 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

**PROJECT DESCRIPTION:** Molecular genetic characterization 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.

**PROGRESS:** We described the molecular genetic basis of Tricho-hepatoenteric syndrome (THES) in Arabs patients with novel mutations of SKIV2 (c.3559\_3579del, p.1187\_1193del) and TTC37 (C4102T, p.Q1368X). Interestingly the congenital presence of café-au-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.

**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 digenic 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.

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

#### KACST FUNDED PROJECTS:

**PROJECT TITLE:** The Pathology 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

**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.

**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

**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 (KACST Project No 08-MED499-20 RAC # 2080 036).

**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

**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).

## RESEARCH PUBLICATIONS

- Novel B4GALNT1 mutations in a complicated form of hereditary spastic paraplegia. Wakil SM, Monies DM, Ramzan K, Hagos S, Bastaki L, Meyer BF, Bohlega S. *Clin Genet*. 2014 Nov; 86 (5):500-1.
- 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.

HUMAN CANCER  
GENOMIC RESEARCH



## HUMAN CANCER GENOMIC RESEARCH

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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. In this regard, 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 done 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.

**Khawla S. Al-Kuraya, MD FCAP**  
DIRECTOR

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Myra M. Maningas

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.

### **SECTION OF EXPERIMENTAL PATHOLOGY AND MOLECULAR ONCOLOGY**

In 2014, we expanded on our clinical findings and were able to identify several dysregulated survival pathways including mTOR survival pathway in papillary thyroid cancer and epithelial ovarian cancer. These pathways were 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 XIAP and FoxM1 has also been identified in breast cancer samples and further investigation and experimentation is ongoing to elicit the role of these genes in breast cancer pathology.

Molecular Oncology 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 2014, we have now used mTOR as a molecular target as they have been found to be dysregulated in PTC and EOC. Dysregulation of mTOR signaling complex has been studied in detail in PTC and 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 PTC and 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.

### **SECTION OF BIOLOGICAL REPOSITORY CENTRE**

The section of 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, -80°C and -20°C 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 2014.

#### **TASKS**

Collect and maintain archives of frozen tissues (normal and neoplastic), serum, paraffin blocks and commercial cell lines.

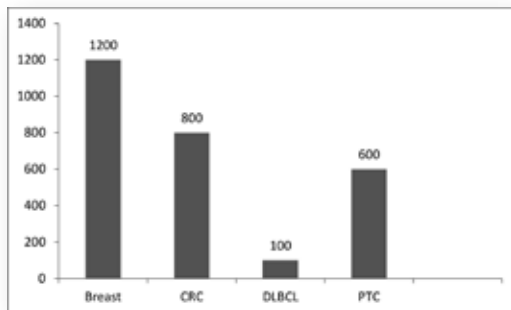
#### **ACTIVITIES**

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 2700

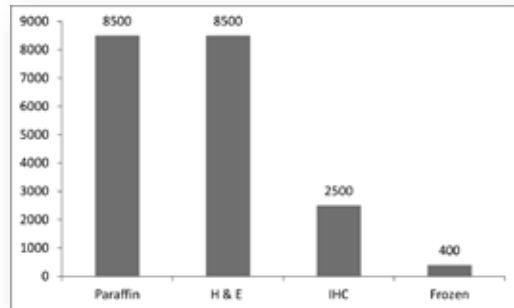
specimens were processed in the year 2013-2014. Five to ten DNA punches obtained for each tumor specimen.

2. Cell blocks prepared from 20 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.

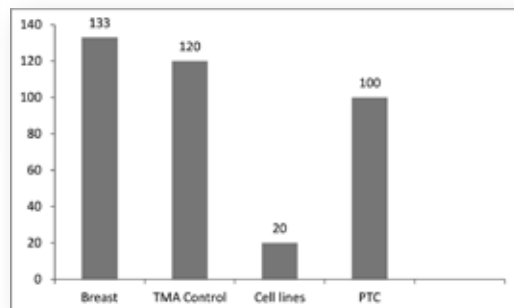
5. Storing biomaterial under controlled temperature:
  - Storage of various commercial cell lines which are being used for various ongoing research projects in our department
  - Maintaining supply of liquid nitrogen for cryomed freezers for department of genetics, Research Centre
6. Maintaining and distributing commercially available cell lines (ATCC) to the research investigator/clinicians with RAC approved projects.



No. 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 373 tumor and normal tissue specimens were arrayed in a TMA format in year 2013-2014. Six to ten TMA replicas obtained for each tumor specimens. In addition we have 3 cell line block TMA.



Tissue microarray construction.

### RESEARCH PROJECTS

**PROJECT TITLE:** The Role of FoxM1 in Saudi Arabian Ovarian Cancer. RAC 2140 033 (NSTIP 10-BIO963-20).

**INVESTIGATORS:** Khawla Al-Kuraya, Shahab Uddin Khan, Shaham Beg, Azhar Hussain, Abdul Khalid Siraj, Maqbool Ahmed, Zeenath Jehan

Grant funded project by the National Science, Technology and Innovation Plan (NSTIP).

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 FoxM1 signaling 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.

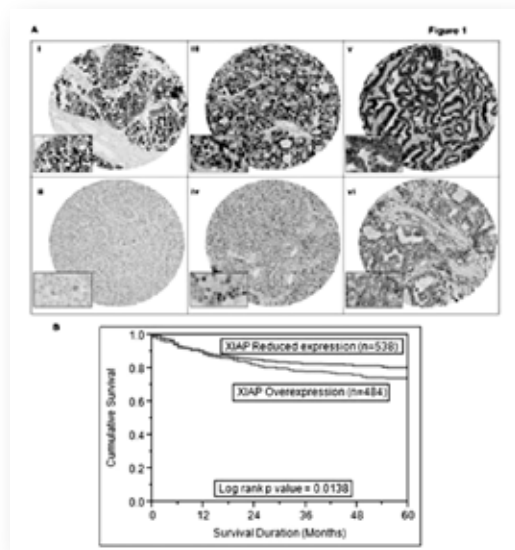
The outcome of this study will provide a better understanding of EOC and should have important clinical implications, as it could result in the development of new and better strategies for targeted therapeutic intervention for the treatment of Saudi Arabian EOC tumours.

**PROJECT TITLE:** Role of XIAP in Pathogenesis of Saudi Arabian Papillary Thyroid Carcinoma. RAC# 2140 010 (NSTIP 11-BIO2219-20).

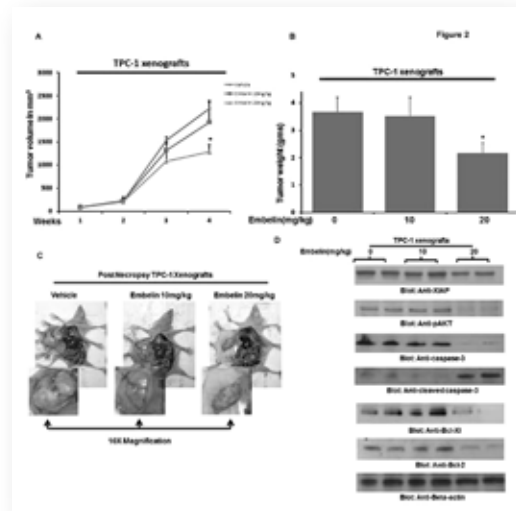
**INVESTIGATORS:** Khawla Al-Kuraya, Shahab Uddin Khan, Azhar Hussain, Rong Bu, Shaham Beg, Abdul Khalid Siraj, Maqbool Ahmed

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 1:** Immunohistochemical (IHC) analysis of PTC clinical samples: (A) PTC array spot showing high expression of XIAP (i), p-AKT (iii) and Bcl-Xl (v). In contrast, another PTC TMA spot shows low expression of XIAP (ii), p-AKT (iv) and Bcl-Xl (vi). 20 X/0.70 objective on an Olympus BX 51 microscope. (Olympus America Inc, Center Valley, PA, USA. with the inset showing a 40X 0.85 aperture magnified view of the same. (B) Survival curves were generated using the Kaplan-Meier method, with significance evaluated using the Mantel-Cox log-rank test PTC with XIAP over expression showed a poor disease free survival of 74.3% at 5 years as compared to 80.6% with low XIAP expression ( $p=0.0138$ ).



**Figure 2:** Inhibition of PTC-cell- tumor-xenografts growth by Embelin. Nude mice at 6 weeks of age were injected subcutaneously with ten million TPC1 cells. (A) The volume of each tumor was measured every week. The average ( $n=5$ ) tumor volume in each group of mice was calculated, \*  $p<0.05$ . (B) After 4 weeks treatment, mice were sacrificed and mean tumor weight ( $\pm$ SD) was calculated in each group. (C) Representative tumor images of each group of mice after necropsy. Inset showing 10X magnification. (D) Whole-cell homogenates from mice injected with TPC1 cells were immuno-blotted with antibodies against XIAP, p-AKT, caspase 3, cleaved caspase 3, Bcl-Xl, Bcl-2 and beta-actin.

**PROJECT TITLE:** Prognostic Significance of CARD10 in Saudi Colorectal Cancers. RAC# 2140 005 (NSTIP 10-BIO959-20).

**INVESTIGATORS:** Khawla Al-Kuraya, Shahab Uddin Khan, Shaham Beg, Azhar Hussain, Abdul Khalid Siraj, Zeenath Jehan, Rong Bu

Grant funded project by the National Science, Technology and Innovation Plan.

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 *In Situ* 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.

**PROJECT TITLE:** Identifying Molecular Signature of Thyroid Cancer Using Next Generation Technology Based on International Cancer Genome Consortium (ICGC) Guidelines. RAC# 2110 031.

**INVESTIGATORS:** Khawla Al-Kuraya, Shahab Uddin Khan, Shaham Beg, Rong Bu, Abdul Khalid Siraj, Abdulrahman Al-Nuaim, Saif Sobhi, Fouad Al-Dayel

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 cataloging 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 Scanscope 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 2000 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 371 clinical samples collected, 85 paired samples of PTC and normal tissue/blood have been sequenced. These include 9 Whole Genome Sequencing and 76 whole exome sequencing. Data analysis of all these sequenced samples is under process by our bioinformatics team and we are expecting a lot of genetic information to be

deciphered. Data generated from this analysis will be used for identifying molecular signatures of Saudi thyroid cancers and will be reflected in upcoming publications in high impact journals.

**PROJECT TITLE:** Prognostic Significance of Molecular and Genetic Alterations in Saudi Arabian Breast Cancers. RAC# 2140 008.

**INVESTIGATORS:** Khawla Al-Kuraya, Shahab Uddin Khan, Rong Bu, Shaham Beg, Abdul Khalid Siraj, Sarita Prabhakaran

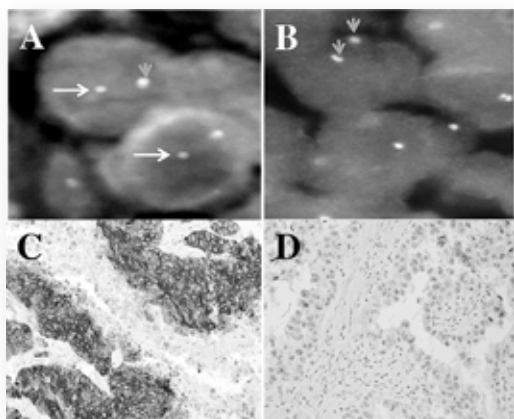
Breast cancer is the most common malignancy among females not only in Saudi Arabia but also worldwide. One million cases are newly diagnosed each year and it remains the main cause of morbidity and mortality among females. There is a dearth of literature on various aspects of breast cancer in Saudi Arabia as most of the studies are done on western population. In this study, we will investigate in detail various clinicopathological parameters along with the molecular and genetic alterations occurring in various signaling pathways and their possible relationships, with special emphasis on PI3K/AKT pathway and hereditary breast cancer. Specifically the hormone receptor status of Saudi Arabian breast cancers, their molecular subtyping and their prognostic significance will be carried out. Molecular alterations of PI3K/AKT pathway and their potential cross-talks with other molecular pathways, with emphasis on PI3KCA amplification and mutational status will be done. This project will also determine the prevalence of hereditary breast cancer and BRCA mutational status in Saudi population and their prognostic implications. Thus this project will provide better understanding of molecular alterations in Saudi breast carcinogenesis and will have important clinical implications, as it could result in development of new therapeutic molecular targets for treatment of Saudi Arabian breast cancers and relatively untreatable subtypes. BRCA analysis will define high risk individuals and may lead to development of effective screening programs for early detection in our ethnic population.

**PROJECT TITLE:** Identification of c-Met Expression and Its Association With Other Survival Markers for Diagnostic Purposes and Risk Stratification in Saudi Arabian Lung Cancer. RAC# 2120 021.

**INVESTIGATORS:** Khawla Al-Kuraya, Fouad Al-Dayel, Shahab Uddin Khan, Abdul Khalid Siraj, Azhar Hussain, Zeenath Jehan, Prashant Bavi

Lung carcinoma is the fifth common cancer affecting Saudi men. Despite improvement of treatment as well as increased awareness in normal population it is the leading cause of mortality worldwide. Due to poor prognosis of lung cancer, there is an increasing need to find molecular biomarkers which can be utilized for diagnosis, risk stratification, early detection, treatment selection and prognosis as well as monitoring for recurrence. Recent advances in molecular biology have led to the identification of new molecular targets, many of which are Protein kinases. Constitutive activation of these protein kinases, by phosphorylation, has been implicated in contributing to malignant phenotypes in a number of human cancers including lung cancer. This proposal investigates the relationship between c-MET dysregulation and survival pathways such as PI3-kinase/AKT pathway in the pathogenesis of Saudi lung cancer. One of the newly identified molecular targets is epidermal growth factor receptor (EGFR) mutations in lung cancer. Dramatic response has been achieved with EGFR inhibitors in lung cancer expressing corresponding targets. However, cancer cells acquire resistance to these drugs and cause recurrence. This has been attributed to other dysregulated survival pathways such as MET kinase. Recently, translocation of the anaplastic lymphoma kinase (ALK) gene is also found to play a predictive role in adenocarcinoma tumor genesis. Recent studies utilizing Crizotinib – a dual ALK and MET inhibitor has shown promising results in clinical trials in patients from the western population who can benefit from targeted therapy. However, no data are available on the prevalence of ALK rearrangement changes in Middle Eastern population. In this study we have investigated ALK

gene rearrangement which can identify patients with adenocarcinoma who are sensitive to Met inhibitors. ALK gene rearrangements were studied using fluorescence *in situ* hybridization (FISH) on 97 adenocarcinoma samples utilizing microarray format. Ninety seven lung adenocarcinoma cases were evaluated. There were 3 cases exhibited ALK gene rearrangement (3%). All of these 3 cases were moderately differentiated adenocarcinoma. None of our cases showed signet cells or abundant intracellular mucin. The findings of this study show that incidence of ALK in adenocarcinoma of the lung is similar to the published western data and these patients can benefit from targeted therapy like Crizotinib; a dual ALK and MET inhibitor that have shown promising results in clinical trials. Further studies are looking specifically whether inhibition of c-MET with pharmacological inhibition or siRNA knock down strategy can affect the expression of other survival pathways such as PI3-kinase/AKT pathway or pro-survival molecules such as XIAP and Survivin.



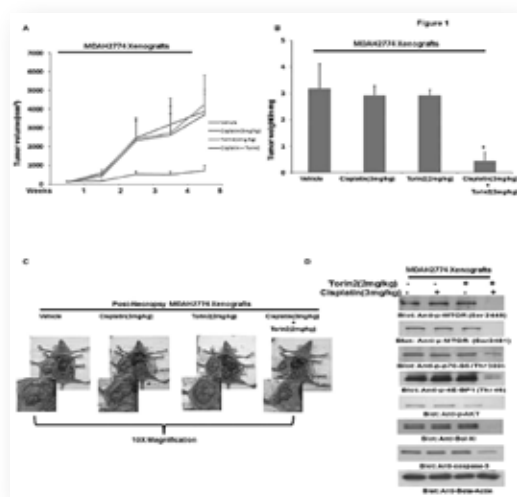
**Figure 3:** Photomicrographs of ALK gene rearranged representative samples. A. FISH performed on Lung tumor cells showing ALK rearrangement with ALK break-apart probe from Vysis. White arrow indicates red rearranged. ALK signal, yellow arrowhead indicates red and green fused normal ALK gene. B. FISH performed on Lung tumor cells without ALK rearrangement utilizing ALK break-apart probe from Vysis. Yellow arrowhead indicates red and green fused two normal ALK genes. C. ALK protein expression by immunohistochemistry performed on lung tumor tissue. D. Absence of ALK protein expression by immunohistochemistry performed on lung tumor tissue.

**PROJECT TITLE:** Anti-Tumor Activity of XIAP Inhibitor Embelin on Mice Xenografts of Epithelial Carcinomas. RAC# 2110 025.

**INVESTIGATORS:** Khawla Al-Kuraya, Shahab Uddin Khan, Prashant Bavi, Maqbool Ahmed, Azhar Hussain

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 NF $\kappa$ B, 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*. In this study we have generated preliminary data using epithelial ovarian carcinoma cell line MDA2774 in nude mice. For the xenograft study, female mice were inoculated subcutaneously into the right abdominal quadrant with 10 million MDAH2774 cells in 200 $\mu$ L PBS and divided into 4 groups and treated with Torin2, cisplatin or a combination of both. After 5 weeks of treatment, mice were sacrificed and individual tumors were weighed, and then snap frozen in liquid nitrogen for storage. As shown in Figure 1A. Torin2, Cisplatin combination treatment causes a time dependent regression of MDAH2774 xenograft tumors in mice as compared to Vehicle, Torin2 and Cisplatin alone treated mice. A significant reduction in

tumor weight (Figure 1B) was also observed at this treatment condition. Additionally, images of tumor after necropsy showed that combination Torin2 and Cisplatin treatment resulted in shrinkage of tumor size (Figure 1C). As shown in Figure 1D, the decrease in tumor volume and size was due to induction of apoptosis by the combination of Torin2 and Cisplatin treatment as indicated by decrease expression and down-regulation of p-mTOR(ser2448), pmTOR(ser2481), p-p70-S6(Thr389), p-4E-BP1(Thr46), p-AKT, Bcl-Xl, and Caspase-3. These data suggest that combination of Torin2 and Cisplatin in xenograft treatment is also effective against xenografts of MDAH2774 cell in shrinking the tumor size via down regulation the above mentioned proteins.



**PROJECT TITLE:** Prognostic significance of genetic alterations in Saudi Colorectal Cancers. RAC# 2080 030.

**INVESTIGATORS:** Khawla Al-Kuraya, Shahan Uddin Khan, Maqbool Ahmed, Abdul Khalid Siraj, Zeenath Jehan, Rong Bu, Azhar Hussain, Mehar Sultana

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.

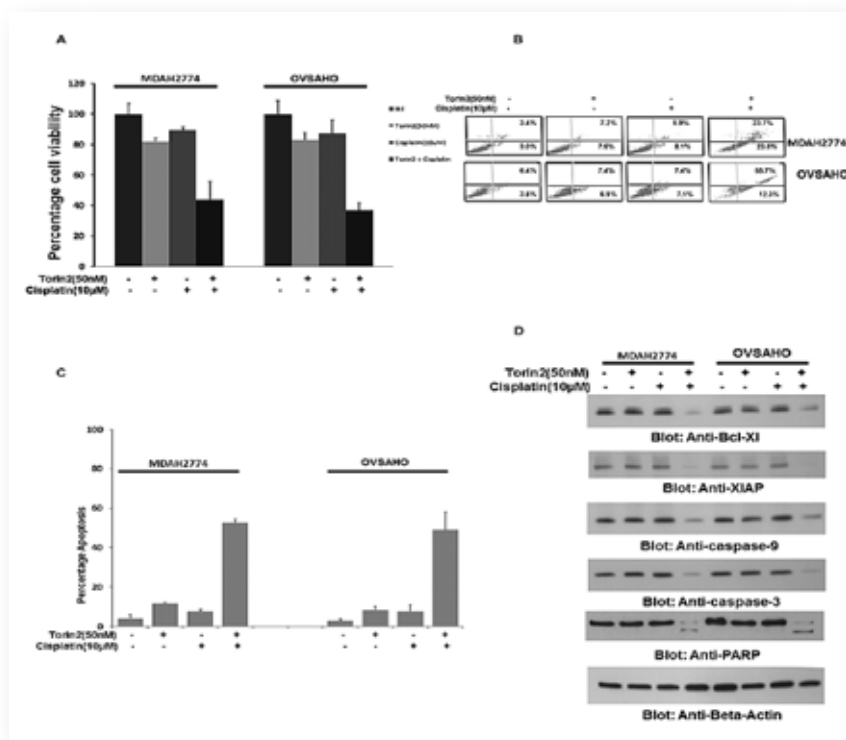
Colorectal cancer (CRC) is one of the common cancers in the world. In Saudi Arabia, CRC is the most common cancer in males and third most common in females. A newly proposed integrated pathways comprising traditional, alternate and serrated by genetic and epigenetic factors was defined recently and hypothesized 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:** Cyclooxygenases: Target for Epithelial Ovarian Cancer Prevention and Treatment. RAC# 2080 029.

**INVESTIGATORS:** Khawla Al-Kuraya, Shahab Uddin Khan, Azhar Hussain, Rong Bu, Zeenath Jehan, Prashant Bavi

In this project that was previously funded by KACST, we continued to identify and target molecular markers that were found to be associated with Cox2 expression in epithelial ovarian cancer (EOC). Previously, we found that mTOR signaling pathway plays a significant role in EOC and targeting this pathway with a dual mTOR inhibitor; Torin2 inactivates mTOR1 and mTOR2 complexes and its downstream targets. This year, we have continued to study the mTOR pathway in epithelial ovarian cancer (EOC) using the dual inhibitor; Torin2. Previously we had proposed to extend our study to include PI3-kinase inhibitor, LY294002 in combination with Torin2 to induce efficient apoptosis in EOC cell

lines. However, after preliminary experiments, we found that Cisplatin was a better therapeutic option to use as a combination agent to be combined with Torin2 for *in vitro* experiments. Following is the progress that has been made for this study. Our *in vitro* data showed that Torin2 treatment alone could inhibit cell viability via induction of apoptosis at doses of 200 and 400nM. In addition, we also found that Torin2 at dose of 50nM and cisplatin at 10 $\mu$ M could synergistically induce apoptosis in EOC cells via activation of the mitochondrial apoptotic pathway. These set of data reassert our findings that Torin2 has the ability to potentiate the anticancer effect of Cisplatin *in vitro*.



**Figure 5:** Co-treatment with Torin2 and cisplatin inhibit cell viability and induce caspase-dependent apoptosis in EOC cells. (A) MDAH2774 and OVS4HO cells were treated with either 50nM Torin2 in the presence and absence of 10 $\mu$ M cisplatin for 48 hours. Following treatment, cells were analyzed for cell viability by MTT assay as described in material and methods. Bar graph displays the mean  $\pm$  SD (standard deviation) of three independent experiments, \*  $p < 0.05$ , statistically significant (Students t-test). (B and C) MDAH2774 and OVS4HO cells were treated with either 50nM Torin2 in the presence and absence of 10 $\mu$ M cisplatin for 48 hours. Following treatment, cells were stained with fluorescent-conjugated Annexin V/PI and apoptosis was analyzed by flow cytometry. Figure 5D is a bar graph with an average of three independent experiments. (D) EOC cells were treated with either 50nM Torin2 in the presence and absence of 10 $\mu$ M cisplatin for 48 hours. Following treatment, cells were lysed and equal amounts of proteins were immuno-blotted with antibodies against Bcl-Xl, XIAP, caspase-9, caspase-3, PARP and beta-actin.

**PROJECT TITLE:** Molecular Signatures of Diffuse Large B-cell Lymphoma (DLBCL), Lung and Ovarian Cancer: A Pilot Study. RAC # 2060 008.

**INVESTIGATORS:** Khawla Al-Kuraya, Hassan El-Solh, Asim Belgaumi, Fouad Al-Dayel, Shahab Uddin Khan, Zeenath Jehan, Prashant Bavi, Azhar Hussain, Abdul Khalid Siraj

The clinical course of individual cancers are 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.

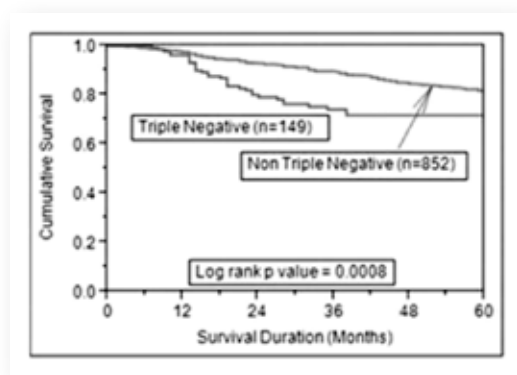
**INVESTIGATORS:** Khawla Al-Kuraya, Abdulrahman Al-Nuaim, Shahab Uddin Khan, Azhar Hussain, Maqbool Ahmed, Abdul Khalid Siraj, Rong Bu

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**

Due to the fact that breast cancer in general and TNBC in particular may behave differently in various ethnic groups and because of scarcity of data from this ethnic population, we, in this study have extensively characterized a large cohort of breast cancer tissue to determine the incidence of TNBC in breast cancer patients of Saudi Arabian origin. We have further correlated TNBC with various clinical parameters to identify the risk factors and prognosis of these aggressive cancers. Finally, we have investigated the status of EGFR and PARP expression by immunohistochemistry in our cohort of TNBC to see whether targeting EGFR and PARP using specific inhibitors and/or monoclonal antibodies could be a viable therapeutic option in the management of these aggressive breast cancers. Incidence of Triple Negative Breast Cancer (TNBC) in Saudi female population was 14.9% (149/1001) and associated with aggressive phenotype and high EGFR and PARP expression and a high percentage of TNBC with co-expression of both PARP and EGFR. Survival analysis showed that TNBC group showed significantly poor 5-years overall survival

(71.7%) than non-TNBC group ( $p = 0.0008$ ) (Figure). Univariate analysis for prognostic factors associated with 5-years survival in TNBC were high tumor stage, grade and histology. However in multivariate analysis using Cox proportional hazard model, TNBC failed to retain its prognostic value thereby indicating that it is not an independent prognostic marker for poor overall survival. There was no difference in survival between TNBC cases having co-expression of PARP and EGFR as compared to those TNBC not expressing them.



**Figure 6:** Kaplan Meyer survival curve of TNBC patients showing poor overall 5 year survival of TNBC as compared to non-TNBC cases of breast cancer.

### Colorectal Cancer

In this project we have investigated the genetic alterations of anaplastic lymphoma kinase (ALK) in colorectal cancers of Saudi Arabia. Recently, (ALK) has been found to be altered in several solid and hematological tumors. Crizotinib; a dual ALK and MET inhibitor that has shown promising results in clinical trials in lung cancer patients with ALK gene alterations. ALK gene copy number changes and mutations in colorectal cancers (CRC) are not well characterized. We aimed to study the prevalence of ALK copy number changes, translocations, gene mutations and protein expression in 770 CRC patients and correlate these findings with molecular and clinico-pathological data. We were unable to find any mutation in the ALK or translocations

however, we found a very low incidence 3.4% of CRC had copy number gain, which were associated with poor prognosis( $p=0.0135$ ). This study reveals a significant impact of ALK gene copy number alterations on the outcome of patients with CRC. The findings of our study highlight a potential role of targeting ALK in advanced colorectal cancers by using ALK FISH and ALK IHC as a screening tool to detect ALK alterations. Based on these findings, the potential role of ALK inhibitor as a therapeutic agent in a subset of CRC merits further investigation.

### RECENT ACHIEVEMENTS

The researchers at the Human Cancer Genomic Research (HCGR) continue to pursue the challenges in the field of Cancer Research and working on their mission which is to conduct translational research on cancers that are more prevalent in the Kingdom of Saudi Arabia.

#### These are our major achievements for Year 2014:

1. The analysis of 100 papillary thyroid cancer cases identifying novel mutations as a part progress of the International Cancer Genome Consortium (ICGC) project.
2. Determination of the role of XIAP in Papillary Thyroid Cancer.
3. Investigation and identification of the MTOR signaling pathway as a potential diagnostic marker and therapeutic target for the management of epithelial ovarian cancer, papillary thyroid cancer and colorectal carcinoma.
4. Identification and targeting molecular markers such as XIAP and FoxM1 for the management of breast cancer.
5. Identification of low incidence of BRAF mutations in Middle Eastern colorectal carcinoma.
6. Identification of the role of PTEN in triple negative breast cancer.
7. Characterization of the molecular pathways in colorectal carcinoma.
8. Identification of the role of ALK alteration in breast cancer.

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DEPARTMENT OF  
INFECTION AND IMMUNITY



## DEPARTMENT OF INFECTION AND IMMUNITY

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The Department of Infection and Immunity reached its final composition in January 2012. It now constitutes four research sections, namely Immunocompromised Host (IH), Microbial Pathogenesis (MP), Molecular Virology (MV), and Mycobacteriology (MB).

Mohammed N. Al-Ahdal  
CHAIRMAN

### MEMBERS

Ahmed A. Al-Qahtani  
Sahal A. Al-Nakhli  
Mohammed G. Elfaki  
Maha A. Al-Mozaini  
Alwaleed A. Alaidan  
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Maureene P. Delos-Reyes  
Jorge P. Bautista

### GRANT FUNDED EMPLOYEES

Hanan M. Shaarawi  
Nisreen Z. Khalaf  
Walaa K. Al-Arnous  
Alria R. Datijan  
Iram Saba Wani  
Mary Grace D. Fernandez  
Rawan A. Al-Romaih

In the IH Section, we aim to define the molecular pathways of HIV-1 and HIV-2 immune protection in patients and analyze the virologic and immunologic characteristics of the HIV-1 and HIV-2 in this region. In addition, we plan to define the immunological and molecular pathways that governs immune deficiency in patients undergoing solid organ transplantation. In the MP Section, research is currently focused on the host response to *Brucella melitensis* infections, and the genetic response of *Plasmodium falciparum* to drug treatment. These efforts are essential to search for drugs and/or vaccine targets. DNA fingerprinting of bacteria causing nosocomial infections is offered as a service to the hospital. In the MV Section, our research activities focus on blood-borne hepatitis viruses (HBV and HCV), human papillomaviruses (HPV), and seasonal respiratory viruses. The prevalence of HPV and its association with cervical cancer will provide the public and appropriate government agencies with information vital for assisting in the decision to recommend HPV screening, triage, and vaccination as well as aid in the prediction of the disease progression. In the MB Section, molecular studies on *Mycobacterium tuberculosis* are conducted to elucidate the strains found in the community and investigate the anti-tuberculosis drug resistance. Non-tuberculous *mycobacterial* infections are also investigated. These studies will provide research-based information to decision makers to enable them to draw strategies to control *mycobacterial* infections.

## APPROVED PROJECTS

**PROJECT TITLE:** Functional Properties of Dendritic Cells in Saudi HIV-1 Elite Controllers.

(RAC # 2111-001, KACST Project # P-L-11-0105, funded SR1,311,470.00)

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-1. Most prior studies have focused on the analysis of T- and B- cell responses in these patients, however, it is now clear that such classical adaptive immune responses alone are not the major reason for undetectable viremia in these patients. Dendritic cells, a key element of the innate immune system, play a central role in structuring host immunity<sup>3</sup>, 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 (1) the analysis of phenotypic and functional properties of myeloid and plasmacytoid dendritic cells in HIV-1 infection, and (2) the assessment of the functional regulation of dendritic cells from elite controllers by Leukocyte immunoglobulin Like receptors.

**PROJECT TITLE:** Modeling of Immunosuppression and Clinical Trials in Renal Transplantation.

(RAC # 2111-005, KACST Project # A-T-34-239, funded SR1,400,345.00)

This is to establish 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:** Investigating the Possible Role of the Mutated Gene(s) in Aicardi-Goutieres Syndrome in HIV Infection.

(RAC # 2111-001)

Aicardi–Goutiere syndrome (AGS) is a hereditary neurodegenerative disorder characterized mainly by early onset progressive encephalopathy, concomitant with an increase in interferon- $\alpha$  (IFN- $\alpha$ ) 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- $\alpha$ -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 study the possible role of the mutated gene(s) in AGS patient seen within KFSHRC-RUH to (1) investigate the relation and the roles of these the mutated gene(s) in the suppression of retroviral infections, and (2) 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, KACST Project # A-T-0117, funded SR47,000)**

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 proteosomal degradation of SAMHD1, which will lead to the increase of HIV infection in non-permissive cells such as dendritic cells. 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: Development of Anti-MERS Corona Virus Hyper Immune Product.**

**(RAC# 2140-025)**

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 intravenous-immunoglobulin 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: Understanding the Role of Innate Immune Humoral Factor in HIV-1.****(RAC# 2140-032)**

HIV-1 is a disease of immunosuppressed and immunocompromised subjects. Its 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, 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. 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. 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: Prediction of Invasive Fungal Infection in BMT Patients.****(RAC# 2140-034)**

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: Modulation of the Host Cell Proteome in Patients With Active Brucellosis.****(RAC# 2110 040, KACST Project # AT-32-24, funded SR1,369,500)**

Current treatment regimens against brucellosis are not optimal due to the persistence of *brucellae* inside macrophage. There is no vaccine available to prevent human infection with *brucellae*. Therefore, there is an urgent need to pursue the development of novel drugs and/or vaccine targets against human brucellosis. With the advent of functional genomics and proteomics, these goals can be achieved by using differential expression and functional analysis of proteins involved in host-pathogen interactions. In this proposal, a database for host proteins that are consistently being modulated following infection with *B. melitensis* will be identified and characterized

by using two-dimensional gel electrophoresis and MALDI-TOF mass spectrometry. Comparison of fingerprints from experimentally generated peptides-mass with algorithms predicting protein localization from the sequenced genome of *Brucella*, can be used to define important proteins involved in virulence, signal transduction, and immune regulation. *Brucella* polypeptides that were separated by SDS-PAGE and electroelution will be examined for their ability to induce lymphocyte proliferation and IFN- $\gamma$  production in patients with brucellosis. The effects exerted by these polypeptides will be subsequently evaluated by lymphocytes blastogenesis and IFN- $\gamma$  mRNA-specific PCR or ELISA in order to elucidate *brucella*-T cell epitopes as putative vaccine targets.

**PROJECT TITLE: Hepatitis C Virus Genotype 1: How Genetic Variability of the Core Protein Affects the Response to Pegylated-Interferon and Ribavirin Therapy.**

(RAC# 2090001, KACST Project # ARP-30-38, funded SR1,442,000.00)

Hepatitis C virus subgenotypes 1a and 1b are found worldwide and cause 60% of all hepatitis C cases. It has been reported recently that viral genetic variations have a critical impact on the patient treatment outcome. In particular, polymorphisms of the HCV core protein have been linked to poor treatment response. However, most of these studies were conducted on Asian populations, Japanese in particular who are infected with HCV subgenotype 1b. Hence, we aimed in this study to examine the core protein polymorphisms in Saudi patients who are infected with chronic HCV genotype 1 (1a and 1b subtypes) and its association with treatment outcome. Direct sequencing of full-length core protein and data mining analyses were utilized. Results have shown that the response to treatment is dependent on subgenotypes. Indeed, HCV-1b showed different point mutations that are associated with treatment outcome where the point mutations at positions 70 (Arg(70) Gln) and 75 (Thr (75) Ala) in HCV-1b are significantly associated with PEG-IFN/

RBV treatment response. In contrast, HCV-1a showed no significant association between core protein mutations and response to treatment. In addition, analyses of HCV-1a core protein sequences revealed a highly conserved region especially in the responder group. This study provides a new insight in the genetic variability of full-length core protein in HCV genotype 1 in Saudi infected patients.

**PROJECT TITLE: 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.**

(RAC# 2090001, KACST Project # ARP-30-38, funded SR1,442,000.00)

Hepatitis C virus (HCV) shows a remarkable genetic diversity, contributing to its high persistence and varied susceptibilities to antiviral treatment. Previous studies have reported that the substitution of amino acids in the HCV subgenotype 1b core protein in infected patients is associated with a poor response to pegylated interferon and ribavirin (PEG-IFN/RBV) combined therapy. Because the role of the core protein in HCV genotype 4 infections is unclear, we aimed in this study to compare the full-length core protein sequences of HCV genotype 4 between Saudi patients who responded (SVR) and did not respond (non-SVR) to PEG-IFN/RBV therapy. Direct sequencing of the full-length core protein and bioinformatics sequence analysis was utilized. Our data revealed that there is a significant association between core protein mutations, particularly at position 70 (Arg70Gln), and treatment outcome in HCV subgenotype 4d patients. However, HCV subgenotype 4a showed no significant association between core protein mutations and treatment outcome. In addition, amino acid residue at position 91 was well-conserved among studied patients where Cys<sup>91</sup> is the dominant amino acid residue. These findings provide a new insight into HCV genotype 4 among affected Saudi population where the knowledge of HCV core gene polymorphisms is inadequate.

**PROJECT TITLE:** Human Papillomavirus Viral Load and E6/E7 mRNA Expression as Predictive Markers for the Development of Cervical Carcinoma.

(RAC# 2130033, KACST Project # 13-MED2127-20, funded SR1,783,000.00)

Our research activities focus on the prevalence of the human papillomavirus (HPV) and its association with cervical cancer. This line of research will contribute greatly to the global knowledge about the occurrence of this sexually transmitted agent. Our results may also provide the public and appropriate government agencies with information vital for assisting 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 on HPV type and transcriptional activities. The overall goal of our proposed study is to determine whether the presence of a high HPV viral load and the mRNA expression of E6/E7 oncogenes correlate with disease progression. The specific aims are as follows: (1) Examine cervical specimens from participating Saudi women for normal and abnormal cytology, classifying the stages of abnormal cytology according to the Bethesda classification. (2) Identify HPV DNA through PCR amplification of the L1 gene, and genotype HPV-positive results using the bead-based multiplexing Luminex assay. (3) Sequence the whole HPV genome to establish phylogenetic analyses of the HPV strains occurring in a Saudi population. (4) 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. (5) Perform quantitative real-time reverse transcription PCR assays that detect and quantify E6/E7 oncogene mRNA to determine whether these oncogenes are predictive markers for the development of cervical carcinoma.

**PROJECT TITLE:** The Association of Toll-Like Receptor 4 Polymorphism With Hepatitis C Virus Infection in Saudi Arabian Patients.

(RAC # 2060040, KACST Project # ARP-27-18, funding SR875,000.00)

Hepatitis C Virus (HCV) is a single stranded RNA virus. It affects millions of people worldwide and is considered as a leading cause of liver diseases including cirrhosis and hepatocellular carcinoma. A recent study reported that TLR4 gene polymorphisms are good prognostic predictors and are associated with protection from liver fibrosis among Caucasians. This study aims to investigate the implication of genetic polymorphisms of TLR4 gene on the HCV infection in Saudi Arabian patients. Two SNPs in the TLR4 gene, rs4986790 (A/G) and rs4986791 (C/T), were genotyped in 450 HCV patients and 600 uninfected controls. The association analysis confirmed that both SNPs, showed a significant difference in their distribution between HCV infected patients and uninfected control subjects ( $p < 0.0001$ ; OR= 0.404, 95% CI= 0.281-0.581) and  $p < 0.0001$ ; OR=0.298, 95% CI= 0.201-0.443), respectively. More importantly, haplotype analysis revealed that four haplotypes, AC, GT, GC, and AT (rs4986790, rs4986791), were significantly associated with HCV infection when compared with control subjects. One haplotype AC was more prominently found when chronic HCV-infected patient were compared with cirrhosis/HCC patients (frequency = 94.7% and  $p = 0.04$ ). Both TLR4 SNPs under investigation were found to be significantly implicated with HCV-infection among Saudi Arabian population.

**PROJECT TITLE:** Molecular Characterization of HBV X Gene in Saudi Arabia.

(RAC # 2060040, KACST Project # 11-MED1430-20, funded SR1,732,000.00)

The aim of this project was to investigate the prevalence and pattern of HBV X gene mutations and their clinical significance in different categories of infections among Saudi patients. Analysis of the HBx gene polymorphism showed that mutations in the amino acid sequence at positions V88F, H94Y, S42P

and A47T were observed in all categories (in-active, active, cirrhotic and HCC). They were found to be similar to other studies and have been proposed as prognostic markers for the development of liver cancer suggesting that these changes will occur at an earlier stage of the disease and gradually increase the risk of HCC. The double mutation K130M + V131I and triple mutations I127T + K130M + V131I and K130M + V131I + F132Y were significantly more common in our studied HCC population. Regardless of the genotype, the mutations shared the same site or region of the X gene; other mutational sites were observed common to all categories that were uncommon in previous studies.

**PROJECT TITLE: Detection of Interferon Gamma Production for the Diagnosis of Latent Tuberculosis in Health Care Workers at King Faisal Specialist Hospital and Research Centre.**

(RAC# 2091046)

Health care workers (HCW's) are among high risk groups whom might get the TB infection. The traditional diagnostic method which is in use to detect latent infection among health care worker is Mantoux- PPD test. However, we believe that Interferon Gamma Release Assays (IGRA, QuantiFERON-TB gold test) is more specific and sensitive in comparison to PPD test to detect MTB infection. As a result, this project was designed to evaluate the QuantiFERON-TB gold test as a new diagnostic tool to screen the HCW's for MTB infection. Eventually IGRA data generated from this project will be compared with the efficacy of PPD test. A decision will be made to use such test as additional or alternative tool.

**PROJECT TITLE: Evaluation of QuantiFERON-TB Gold in Patients With Extrapulmonary Tuberculosis.**

(RAC# 2091006)

Extrapulmonary tuberculosis (EPTB) prevalence is on a rise globally and also in Saudi Arabia. Diagnosing

extrapulmonary TB (EPTB) is not easy and sometimes need invasive procedures. In another occasion, EPTB may be confused with other diseases because of the similarity in clinical presentations. The diagnostic value of IGRA's for the diagnosis of EPTB has not been well analyzed. In this project, we are trying to evaluate QuantiFERON-TB Gold test as a tool to diagnose or at least exclude or include suspected extrapulmonary cases.

**PROJECT TITLE: Detection of Interferon Gamma Production to Diagnose Latent Tuberculosis in Patients for Kidney Transplant.**

(RAC# 2070013)

Interferon gamma release assay (IGRA) has been shown to be more specific and sensitive for the detection of latent TB in immunocompetent individuals. However, data are scarce concerning the performance of IGRA in immunosuppressed individual non-reactive to HIV. This project is targeting to evaluate QuantiFERON TB gold test as the new diagnostic tool to detect dormant TB in the very vulnerable group- kidney transplant patients. The relative performance of IGRA against PPD will be compared.

**PROJECT TITLE: Genome Sequencing to Characterize Unknown Mutations and Identify the Phylogeny of Unknown Drug Resistant *Mycobacterium Tuberculosis* Strains Causing an Ongoing Transmission in Saudi Arabia.**

(RAC# 2130020, KACST Project # 11-Bio1436-20, funded SR1,996,000.00)

The increasing incidence of drug resistant tuberculosis is a threat to any tuberculosis control program. The current reports show Saudi Arabia is not an exception with 23.5% of overall drug resistance and in particular 4.5% overall rate of multi-drug resistant tuberculosis (MDRTB). Recent studies showed, that a considerable amount (up to 18.9%) of *Mycobacterium tuberculosis* are not defined into

known phylogenetic lineages circulating in the country, which includes isolates resistant to one or more of the first line drugs. This project has been designed to carry out an in-depth analysis of the determinants of MDRTB in Saudi Arabia. This study will define the drug resistance mechanisms in strains which were reported as unknown when commercial assays were used. An in-depth analysis of the phylogenetic position of strains not allocated to define main lineages, and the magnitude of recent transmission of MDRTB strains across Saudi Arabia by using next generation genome sequencing are under way.

**PROJECT TITLE: Epidemiology and Genetic Diversity of Non-Tuberculous Mycobacteria in Saudi Arabia.**

**(RAC# 2130021, KACST Project # MED-3172-20, funded SR1,993,000.00)**

Non-tuberculous *Mycobacteria* (NTM) are usually saprophytes found in natural sources, but almost 50 species of them are found to be pathogenic to humans. Human to human transmission is rarely reported so the pathological consideration of these *Mycobacterial* groups was limited before. But the emergence of AIDS and many other immune-suppressive ailments including transplantations, leukaemia, auto-immune diseases, cancer, and treatment conditions [chemotherapy] at the recent time made, NTMs as an emerging opportunistic pathogenic bacterial group. The correct rates of NTM infections in Saudi Arabia are still unknown except for some case reports. Therefore, the project's main objectives are to extensively evaluate the epidemiology of NTM in different regions of the country and to define the genetic diversity of the common species. These will be accomplished by (1) determining the rate of NTM infections at national level, and (2) identifying all the species of the NTM presented and studying the genetic heterogeneity of common species.

**PROJECT TITLE: Genotyping *Mycobacterium Tuberculosis* from Patients With Extrapulmonary Tuberculosis.**

**(RAC# 2090014, KACST Project # AT-34-103, funded SR1,176,000.00)**

Extrapulmonary tuberculosis is a significant component of all tuberculosis burdens. It has been recently reported more often due to various reasons. The changes in populations, health care services, and possibly that the pathogen have contributed to the increase in extrapulmonary tuberculosis, locally and globally. Data on extrapulmonary tuberculosis epidemiology using molecular genotyping techniques are scarce. Thus we proposed to genotype the isolates of *Mycobacterium tuberculosis* from patients with extrapulmonary tuberculosis. The patterns of genotypes will be compared to existing patterns from local and international repositories.

**PROJECT TITLE: Detecting *Mycobacterium tuberculosis* by Molecular Techniques in Transplanted Organs.**

**(RAC# 2130031, KACST Project # AT-34-146, funded SR1,200,000.00)**

It is estimated that one-third of the world's population carries latent tuberculosis, and millions of cases of reactivated tuberculosis are predicted in the coming years. Not all patients infected with tuberculosis progress to active infection, and some remain with latent TB infection. However, up to ten percent may progress to active infection. Although tuberculosis is uncommon among transplant recipients, the risk of tuberculosis 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. Transmission of the infection through organs transplanted from individuals infected with *Mycobacterium tuberculosis* is possible. We proposed to test the transplanted organs (livers and kidneys) for *Mycobacterium tuberculosis* DNA by molecular techniques (PCR in Situ Hybridization) and to identify the implications of positive *M. tuberculosis* DNA in transplanted organs in the recipient host.

**SELECTED ACHIEVEMENTS**

- Collaboration with many institutional, national and international scholars
- Creation of the first HIV/AIDS research laboratory within the Kingdom
- Development of HIV-2 viral load assay using a real-time RT-PCR method
- Awarding of two scholarships from KFSHRC for the enrollment of Global Clinical Scholars Research Training Program (GCSRT), Harvard Medical School, Boston, MA, USA, along with diploma of completion of the two DII staff
- Establishment of the REDcap database for KFSHRC-RUH
- Membership in different AIDS programs in NIH (USA) and in NIBSC (UK)
- Setting up the initial phase HIV/AIDS and Cervical Cancer Awareness Campaign
- Involvement in various institutional, national and international committees and editorial boards
- Genotype analysis of nosocomial infection outbreaks
- Participation in the final defense of dissertations for graduate degrees in various institutions
- Role of variations in HCV genome in response to standard treatment

**SELECTED PUBLICATIONS 2014**

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- (2014) Novel type of VanB2 teicoplanin-resistant hospital-associated *Enterococcus faecium*. *International Journal of Antimicrobial Agents* 44(2): 156-9.
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THE DEPARTMENT OF  
MOLECULAR ONCOLOGY



## MOLECULAR ONCOLOGY

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**T**he 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 Molecular Carcinogenesis.

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.

**Abdelilah Aboussekhra, PhD**

ACTING CHAIRMAN

ADMINISTRATIVE SUPPORT STAFF

**Miss Robin Seamer**

#### **SELECTED ACHIEVEMENTS FOR 2014**

1. We have shown that obesity is a major risk factor for breast cancer among Saudi females.
2. We have identified BRCA1 methylation-related molecular changes, which further confirmed the importance of this epigenetic change as early detection molecular biomarker for breast cancer.
3. IL-6 plays a major role in the cross-talk between breast cancer cells and their microenvironment.
4. The RNA binding protein AUF1 is a major cancer promoting factor, and potential prognostic/predictive marker for different types of cancer.
5. Establishment of the Research Center at KFSH&RC Jeddah.

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## BREAST CANCER SECTION

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Breast cancer is a major cause of morbidity and mortality among females in Saudi Arabia. Clinical observations indicate that 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 diagnostic, 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 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.

**Suad Al-Abdullah (Bin Amer), PhD**

HEAD

MEMBERS

**Amal Kattan, PhD**

**Asmaa Nofal, BSc**

**Safia Madkhali, BSc**

## RESEARCH PROJECTS

**PROJECT TITLE:** Determination of DNA Methylation Profile of Breast Cancer Patients to Develop Diagnostic and Prognostic Biomarkers.

**FUNDING:** The grant for this project was approved by NSTIP (KACST).

**PRINCIPAL INVESTIGATOR:** Suad Al-Abdulla (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 peri-menopause group and a post-menopause group of Saudi breast cancer patients

**PROJECT TITLE:** Micro-RNAs as Biomarkers for Diagnosing Breast Cancers.

**RAC #2110016**

**INVESTIGATORS:** Suad Mohamed (Bin Amer) P.I and Amal Qattan P.I

**PROJECT DESCRIPTION:** Breast Cancer remains one of the commonest cancers affecting women worldwide. To date several genetic, epigenetic (e.g. DNA methylation), 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 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, 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 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.

**PROGRESS:** 8 ml of blood samples was obtained from 50 patients with breast cancer after obtaining appropriate informed consent according to the guidelines detailed by the Ethical Review Committee and 50 controls (for controls, we used in our sample subject who had given blood donor consent for research use).

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## ABSTRACTS

- Al-Jammaz, B. Al-Otaibi, S. Okarvi and S. Amer, Novel Synthesis and Preclinical Evaluation of Folic Acid Derivatives Labeled with <sup>18</sup>F[FDG] for PET imaging of Folate Receptor-Positive Tumors, EANM, Birmingham, UK, October 2011.
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## CANCER BIOLOGY & EXPERIMENTAL THERAPEUTICS

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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 currently elucidating the role of BRCA1 methylation in the predisposition to breast cancer and its potential use as predisposition biomarker. We are also investigating the role of breast stromal fibroblasts and p16 in breast carcinogenesis. In addition, we assess the anti-carcinogenic effect of PAC (a curcumin analogue) 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.

**Abdelilah Aboussekhra, PhD**  
HEAD

MEMBERS

**Nisreen M. Al-Moghrabi, PhD**  
**Huda H. Al-Khalaf, PhD**  
**Mysoon M. Al-Ansary, PhD**  
**Gabriela Silva, PhD**  
**Siti-Faujjah Hendrayani, Msc**  
**Nujoud Al-Yousef, BSc**  
**Huda Al-Howail, BSc**

## RESEARCH PROJECTS

**PROJECT TITLE:** BRCA1 Epimutation and Breast Cancer Predisposition.

**FUNDING:** National Science, Technology and Innovation Plan (NSTIP)

**PROJECT CODE:** 10-BIO1353-20

**INVESTIGATORS:** N. Al-Moghrabi (PI), N. Al-Yousef, S. Ben Amer, T. Al-Tweigeri, A. Tulbah, A. Aboussekhra

**PROJECT DESCRIPTION:** This project has two major aims:

- A. To study whether BRCA1 promoter methylation occurs as germline, with evidence of inheritance, or constitutional, no evidence of inheritance, in early onset breast cancer patients.
- B. To study the molecular significance of the presence of methylated BRCA1 promoter in white blood cells of healthy females.

The major aim is to determine the possible use of BRCA1 promoter methylation in white blood cells as early detection biomarker of breast cancer.

We have recently shown that 14.2% of BC patients and 9.1% of cancer-free females (carriers) harbored methylated BRCA1 promoter in their WBC. Interestingly, 66.7% of patients harbored methylated BRCA1 promoter in both WBC and tumors. Importantly, we have shown the presence of epigenetic changes in 9 other BC-related genes in WBC of both patients and carriers. Additionally, BRCA1 and 15 other important cancer – related genes were found to be differentially expressed in WBC from patients and carriers as compared to controls. Furthermore, we have shown that the carriers exhibited a unique plasma protein pattern different from those of BC patients and controls, with 10 proteins similarly differentially expressed in patients and carriers as compared to controls.

The present results suggest the presence of a strong link between aberrant methylation of the BRCA1 promoter in WBC and breast cancer – related molecular changes, which indicate the potential predisposition of the carriers for developing breast cancer. This informs the potential use of the aberrant methylation of BRCA1 promoter in WBC as a powerful non-invasive molecular marker for detecting predisposed individuals at a very early age.

**PROJECT TITLE:** Investigation of the Role of Stromal Fibroblasts in the Development of Breast Carcinoma: The Tumor Suppressor p1<sup>INK4A</sup> Protein as Target.

**FUNDING:** RAC# 2080009 National Science, Technology and Innovation Plan (NSTIP).

**PROJECT CODE:** MED480-20

**INVESTIGATORS:** A. Aboussekhra (PI), Mysoon Al-Ansary and Siti-Faujjah 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.

**PROJECT TITLE:** Study of the Anti-Cancer Properties of PAC (A Novel Curcumin Analogue) *in Vitro* and *In Vivo*.

**PROJECT CODE:** 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.

**PROJECT TITLE:** Study the Potential Role of IL-6 in the Cross-Talk Between Breast Carcinomas and Their Stromal Fibroblast.

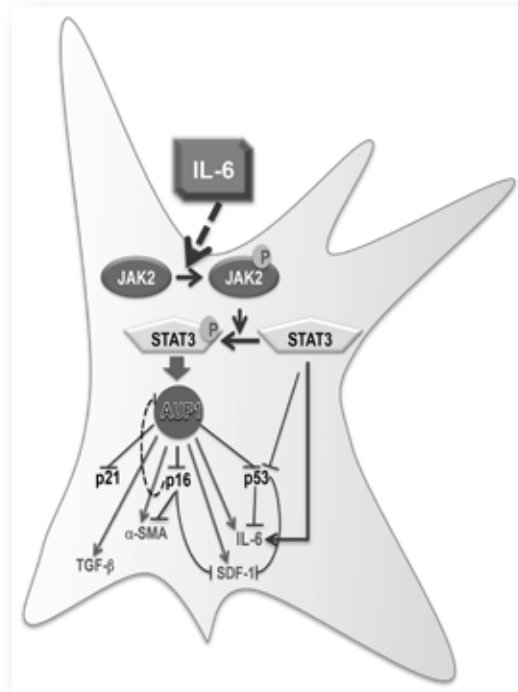
**FUNDING:** RAC# 2120034 National Science, Technology and Innovation Plan (NSTIP), Project.

**PROJECT CODE:** 11-BIO2077-20

**INVESTIGATORS:** A. Aboussekhra (PI), Nisreen Al-Moghrabi, Siti-Faujiah Hendrayani, Gabriela Silva, Huda Al-Howail

**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.

We have recently shown that cancer cells activate their adjacent stromal fibroblasts through the secretion of IL-6, which activates the JAK2/STAT3 pathway. This leads to the upregulation of the RNA binding protein AUF1, which activates the myofibroblast markers SDF1,  $\alpha$ -SMA and TGF- $\beta$ 1 and represses the tumor suppressor genes p16, p21 and p53 (Figure 1).



**Figure 1.** Schematic representation of the role of IL-6 in transactivating breast stromal fibroblasts.

**PROJECT TITLE:** Aging and Cancer: Role of p16/p53 and Stromal Fibroblasts.

**PROJECT CODE:** 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.

### SELECTED ACHIEVEMENTS

- We have shown the presence of a strong link between aberrant methylation of the BRCA1 promoter in white blood cells and breast cancer-related molecular changes. This could be used as a powerful non-invasive molecular marker for detecting predisposed individuals at a very early age.
- We have shown that the tumor suppressor p16 protein negatively regulates the expression/secretion of IL-6.
- IL-6 was identified as playing a major role in the cross-talk between breast cancer cells and their microenvironment.
- The RNA binding protein AUF1 is a major cancer promoting factor, and potential prognostic/predictive marker for different types of cancer.
- Caffeine has anti-breast cancer effects through persistently suppressing the paracrine effects of stromal fibroblasts.

### PUBLICATIONS

- Hendrayani SF, Al-Khalaf HH, Aboussekhra A. The cytokine IL-6 reactivates breast stromal fibroblasts through transcription factor STAT3-dependent up-regulation of the RNA-binding protein AUF1. (2014). *J. Biol Chem.* 289(45):31433-31447.
- Al-Khalaf HH, and Aboussekhra A. MicroRNA-141 and microRNA-146b-5p inhibit the prometastatic mesenchymal characteristics through the RNA-binding protein AUF1 targeting the transcription factor ZEB1 and the protein kinase AKT. (2014). *J. Biol Chem.* 289(45):30962-30976.
- Al-Khalaf HH and Aboussekhra A. ATR controls the UV-related upregulation of the CDKN1A mRNA in a Cdk1/HuR-dependent manner. (2014). *Mol Carcinogenesis.* 53:979-987.
- Nisreen Al-Moghrabi, Asmaa Nofel, Nujoud Al-Yousef, Safia Madkhali, Suad M Bin Amer, Ayodele Alaiya, Zakia Shinwari, Taher Al-Tweigeri, Bedri Karakas, Asma Tulbah and Abdelilah Aboussekhra. (2014). The molecular significance of methylated BRCA1 promoter in white blood cells of cancer-free females. *BMC Cancer.* doi:10.1186/1471-2407-14-830.
- 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.
- Al-Sharif I, Remmal A, Aboussekhra A. Eugenol triggers apoptosis in breast cancer cells through E2F1/survivin down-regulation. (2014) *BMC Cancer.* 13;13:600. doi: 10.1186/1471-2407-13-600.
- Al-Khalaf HH, Mohideen P, Nallar SC, Kalvakolanu DV, Aboussekhra A. The Cyclin-dependent Kinase Inhibitor p16<sup>INK4a</sup> 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<sup>INK4A</sup> Represses the paracrine tumor-promoting effects of breast stromal fibroblasts (2013). *Oncogene* 32 (18) 2356-2364.
- 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. (2013). *J Pathol.* 231:457-465.
- Hendrayani SF, Al-Khalaf HH, Aboussekhra A. Curcumin Triggers p16-Dependent Senescence in Active Breast Cancer-Associated Fibroblasts and Suppresses Their Paracrine Procarcinogenic Effects. (2013) *Neoplasia* 16(6):631-640.

- 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
- Al-Khalaf HH, Aboussekhra A. p16<sup>INK4A</sup> Positively Regulates p21<sup>WAF1</sup> Expression by suppressing AUF1-dependent mRNA decay. (2013) *PloS One*. 23;8(7):e70133.
- Al-Khalaf HH, Hendrayani SF, Aboussekhra A. ATR controls the p21(WAF1/Cip1) protein up-regulation and apoptosis in response to low UV fluences. (2013) *Mol. Carcinog*. 51(12):930-938.
- Karakas B, Colak D, Kaya N, Ghebeh H, Al-Qasem A, Hendrayani F, Toulimat M, Al-Tweigeri T, Park BH, Aboussekhra A. Prevalence of PIK3CA mutations and the SNP rs17849079 in Arab breast cancer patients. (2013) *Cancer Biol Ther*. 14(10): 888-896.



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## MOLECULAR ENDOCRINOLOGY

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The molecular endocrinology section focuses on two main areas. 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 mechanism 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 hereditary endocrine diseases such as hormone resistance syndromes, congenital hypothyroidism, disorders of sex developments, genetic endocrine hypertension and others.

**Ali S. Al-Zahrani, MD, FACP**

HEAD

MEMBERS

**Mai Al-Mohanna, PhD**

**Ebtesam Qasem, BSc**

## RESEARCH PROJECTS

**PROJECT TITLE:** Mutational Profile of Differentiated Thyroid Cancer in Saudi Arabia.

**FUNDING:** RAC Approved

**PROJECT CODE:** 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 have almost completed the work and we are analyzing data and writing manuscripts. A poster was presented last year in the Endocrine Society Meeting/International Endocrine Congress June 2014

**PROJECT TITLE:** mTOR Mutations in Differentiated Thyroid Cancer; Their Prevalence and Correlation With Histopathological Features and Outcome.

**FUNDING:** RAC Approved

**PROJECT CODE:** RAC # 2120 027

**INVESTIGATORS:** Ali S. Alzahrani, MD, Peter Hall, MD, PhD, FRCPath, Hindi Al-Hindi, MD, Mai Al-Mohanna, PhD, Abdelilah Aboussekhra, 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 are investigating the possible mutations in mTOR and their potential roles in the progression of thyroid cancer.

**PROGRESS:** So far, we have sequenced the previously described frequently mutated exons in about 100 cases of differentiated thyroid cancer. We have presented this in the last Endocrine Society Meeting, June 2014. A thesis for the Master student who performed this work is being completed and a manuscript is in progress.

**PROJECT TITLE:** Study of the Molecular Basis of Endocrine Genetic Disorders.

**FUNDING:** RAC Approved

**PROJECT CODE:** RAC# 2130 012

**INVESTIGATORS:** Ali Alzahrani, MD, Afaf Alsagheir, MD, Mohammed Almekthel, MD, Bassam bin Abbas, MD, Mohammed Ahmed, MD, Abdulraof Almahfouz, MD

**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. Two articles were published and around three 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

**PROJECT CODE:** 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 tumorigenesis 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. Known and novel mutations/SNPs have been found. We are analyzing data in terms of its frequency and correlation with the thyroid cancer features. A thesis for the Master student who did the bench work is completed and she is sitting for the Master degree exam soon. A manuscript is being prepared

**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).

**PROJECT CODE:** RAC #2130 034

**INVESTIGATORS:** Ali Alzhrani, MD, Bedri Karkas, PhD, Mai Al Mohanna, Hindi Al Hindi, MD, Mohammed Almehtel, MD

**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. An abstract was submitted to the incoming Endocrine Society meeting, March, 2015.

**PROJECT TITLE:** Molecular Basis of Disorders of Sex Development.

**FUNDING:** National Science, Technology and Innovation Plan (NSTIP) (Grant Program).

**PROJECT CODE:** RAC# 2130 018

**INVESTIGATORS:** Ali Alzahrani, MD, Afaf Alsegehir, 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 an article was published. Several families have been screened and known and novel mutations have been characterized. Some of this work was presented last year (June 2014) in the International Endocrine Congress and the Endocrine Society Meeting. Manuscripts are being prepared.

#### **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. Adrenal Cancer is another area that we got interested in recently and we are planning to explore it further. In addition, our lab is interested in characterizing the molecular basis of some important genetic endocrine disorders that are quite common in our patient population.

#### **PUBLICATIONS**

- Alzahrani AS, Aljuhani N, Qasem E, Almohanna M, Hamoudh E, AlOmair A, Alharbi N 2014 Apparent Mineralocorticoid Excess Caused by a Novel Mutation in 11-beta Hydroxysteroid Dehydrogenase Type 2 Enzyme: Its Genetics and Response to Therapy. *Endocr Pract* 20:e151-156.
- Bin-Abbas B, Al-Humaida D, Al-Sagheir A, Qasem E, Almohanna M, Alzahrani AS 2014 Divergent Gender Identity in Three Siblings with 46XX Karyotype and Severely Virilizing Congenital Adrenal Hyperplasia Caused by a Novel CYP11B1 Mutation. *Endocr Pract* 20:e191-197.
- Xing M, Alzahrani AS, Carson KA, Shong YK, Kim TY, Viola D, Elisei R, Bendlova B, Yip L, Mian C, Vianello F, Tuttle RM, Robenshtok E, Fagin JA, Puxeddu E, Fugazzola L, Czarniecka A, Jarzab B, O'Neill CJ, Sywak MS, Lam AK, Riesco-Eizaguirre G, Santisteban P, Nakayama H, Clifton-Bligh R, Tallini G, Holt EH, Sykorova V 2015 Association Between BRAF V600E Mutation and Recurrence of Papillary Thyroid Cancer. *J Clin Oncol* 33:42-50.
- Zou M, Baitei EY, Alzahrani AS, BinHumaid FS, Alkhafaji D, Al-Rijjal RA, Meyer BF, Shi Y 2014 Concomitant RAS, RET/PTC, or BRAF mutations in advanced stage of papillary thyroid carcinoma. *Thyroid* 24:1256-1266.
- Zou M, BinHumaid FS, Alzahrani AS, Baitei EY, Al-Mohanna FA, Meyer BF, Shi Y 2014 Increased CYP24A1 expression is associated with BRAF(V600E) mutation and advanced stages in papillary thyroid carcinoma. *Clin Endocrinol (Oxf)* 81:109-116

#### **INTERNATIONAL PRESENTATIONS**

16<sup>th</sup> International Congress of Endocrinology/96<sup>th</sup> Endocrine Society Annual Meeting, Chicago, IL, June, 2014

- Oral presentation: Comparison of Differentiated Thyroid Cancer in Pediatric and Adolescents with Young Age Group.
- Poster: Absence of the Most Frequently Reported mTOR Mutations in Thyroid Neoplasms
- 3. Poster: In-Hospital Hyperglycemia Prevalence, Management, Level of Control and Associated Complications and Mortality.
- Poster: Congenital Adrenal Hyperplasia Due to a Previously Undescribed Homozygous Mutation in 17-Alpha-Hydroxylase (CYP17A1) Gene.
- Poster: Thyroid Hormone Withdrawal Time Needed for TSH to Reach 30 Mu/l for Radioactive Iodine (RAI) Remnant Ablation in Differentiated Thyroid Cancer Is Much Shorter Than the Conventional 4-5 Weeks.
- Poster: TERT Promoter Mutations in Follicular-Cell-Derived Thyroid Cancer: Their Frequency and Association with BRAF Mutation, Histopathological Features and Short-Term Outcome.
- Featured poster: Secondary Parathyroid Gland Suppression Is a Major Mechanism for Hypocalcemia in Hungry Bone Syndrome.

## 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

- Chairman, scientific session (PP19/OR19) Metastasis & Tumor Progression; Neoplasia of Endocrine Tissues ((16<sup>th</sup> International Congress of Endocrinology/96<sup>th</sup> Endocrine Society Annual Meeting, Chicago, IL, June, 2014).
- Editorial Board Member: Thyroid, the American Thyroid Association Journal.
- Elected President, The American Association of Clinical Endocrinologists, Gulf Chapter, Abu Dhabi, Oct. 2014.
- Established Research Center at KFSH&RC-Jeddah.
- A mentor of a fellow who won the first and third Annual Research Awards, Department of Medicine, May 2014



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## TRANSLATIONAL CANCER RESEARCH SECTION

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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 into clinical use. We are particularly interested in non-invasive methods to follow up cancer treatment response and early detection of relapses using blood circulation tumor DNA as a biomarker.

Additionally, we are involved in identifying the mutational frequencies of important oncogenes and tumor suppressor genes in the Saudi breast cancer population.

**Bedri Karakas, PhD**  
HEAD

MEMBER

**Areej Al-Zahrani**

## RESEARCH PROJECTS

**PROJECT TITLE:** Identification of the Mutational Spectrum and Frequencies of BRCA1 and BRCA2 Genes in Saudi Breast and Ovarian Cancer Populations.

**FUNDING:** National Science, Technology and Innovation Plan (NSTIP).

**PROJECT CODE:** RAC# 2130 037

**INVESTIGATORS:** Karakas B (P.I), Tweigeri T (CO.I), Colak D (CO.I), Demirkaya O (CO.I), Bin Amer S (CO.I), Tulbah A (CO.I)

**PROJECT DESCRIPTION:** The main aim of this project is to identify the mutational frequency and location of breast cancer susceptibility genes (BRCA1/2) in the 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.

**FUNDING:** National Science, Technology and Innovation Plan (NSTIP).

**PROJECT CODE:** RAC# 2110 020

**INVESTIGATORS:** Karakas B (P.I), Al-Moghrabi N (CO.I), Al-Husaini H (CO.I), Colak D (CO.I), Bin Amer S (CO.I)

**PROJECT DESCRIPTION:** 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 the local breast cancer population as an alternative or a complementary test to the imaging technologies.

**PROJECT TITLE:** The Saudi Arabian Diseaseome. 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 the Therapeutic Outcome for Saudi Diseases.

**FUNDING:** National Science, Technology and Innovation Plan (NSTIP).

**PROJECT CODE:** RAC# 2110 006

**INVESTIGATORS:** Colak D, (P.I), Karakas B (CO.I)

**PROJECT DESCRIPTION:** This is a collaborative project 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 to try to generate some useful predictive, prognostic and surrogate biomarkers to be used during the treatment in the clinic.

**PROJECT TITLE:** Cell Free Fetal DNA (cffDNA) in Maternal Circulation: An Alternative Approach for Non-Invasive Prenatal Diagnosis.

**FUNDING:** National Science, Technology and Innovation Plan (NSTIP).

**PROJECT CODE:** RAC# 20910 01

**INVESTIGATORS:** Karakas B (CO-P.I), Qubbaj W (P.I)

**PROJECT DESCRIPTION:** This is a collaborative project between our section and the IVF section. This project focuses on detecting altered fetal DNZ 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:** 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).

**PROJECT CODE:** RAC# 2120 024

**INVESTIGATORS:** Al-Zahrani A (P.I), Karakas B (CO.I)

**PROJECT DESCRIPTION:** 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 mutation from the tumor. The identified mutations are later used to detect circulating tumor DNZ 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.

#### **SELECTED ACHIEVEMENTS**

- We have shown the PIK3CA oncogene to be highly mutated in Saudi breast cancer population.

#### **PUBLICATIONS**

- Karakas B, Hendrayani F., et al. 2013. Prevalence of PIK3CA Mutations and the SNP rs17849079 in Arab Breast Cancer Patients. *Cancer Biology*, 2013; 14:10, 888.896.
- Garay JP, Karakas B, Abukhdeir AM, Cosgrove DP, Gustin JP, Higgins MJ.,et al. The growth response to androgen receptor signaling in ER $\alpha$ -negative human breast cells is dependent on p21 and mediated by MAPK activation. *Breast Cancer Res.* 2012 Feb 9; 14(1): R27.
- Konishi, H, Mohseni M, Tamaki A, Garay JP, Konishi Y, Karakas B., Mutation of a single BRCA1 allele leads to genomic instability in human breast epithelial cells. *PNAS USA*, 2011; 108(43), 17773-8.
- Kaya N, Colak D, Albakheet A, Abu-Dheim N, Karakas B., et al. A Novel X-linked disorder with developmental delay and autistic features. *Annal of Neurology*, 2012; 71:498-508.



STEM CELL &  
TISSUE RE-ENGINEERING PROGRAM



## STEM CELL & TISSUE RE-ENGINEERING PROGRAM

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**T**he 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 spinal cord injuries, cardiovascular, neurodegenerative, renal and autoimmune diseases, and cancer. The department is working towards achieving the goal of excellence in stem cell research in the Middle East and worldwide. Members of the program are actively participating in basic, pre-clinical and translational clinical research, teaching, and in collaborative projects with the scientific and clinical community. In addition, this program is 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.

**Ayodele A. Alaiya, MB.BS, PhD**  
ACTING DIRECTOR

ADMINISTRATIVE SUPPORT STAFF

**Maria Linda R. Macasieb**

## 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 spinal cord injuries, cardiovascular, neurodegenerative, renal and autoimmune diseases, and cancer. The department is working towards achieving the goal of excellence in stem cell research in the Middle East and worldwide. Members of the program are actively participating in basic, pre-clinical and translational clinical research, teaching, and in collaborative projects with the scientific and clinical community. In addition, this program is 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.

- LIST OF SIGNIFICANT AND SCIENTIFIC ACHIEVEMENTS
- Fourteen (14) on-going RAC approved research projects.
- Three (3) in-house approved project for funding by KACST 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.
- Six (6) Abstracts presented in international scientific conferences/meetings (USA, Greece, Canada, Sweden).

- Four (4) 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 (Mr. Amer Almainan). 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.
- Host "Summer Training Program" for gifted and future scientist students

## COLLABORATORS

### INTERNATIONAL

- Massachusetts General Hospital, USA.
- Brigham and Women's Hospital, Boston, MA, USA.
- Children's Hospital Boston, MA, USA.
- Harvard Medical School, USA.
- Harvard University, USA.
- Massachusetts Institute of Technology (MIT), USA.
- Cancer Center, Karolinska Hospital and Institute, Stockholm, Sweden
- Lund University, Lund, Sweden.
- Dr. Tilanus, Head Molecular Lab at Utrecht University, Netherlands to utilize high-resolution method for HLA typing.
- Prof Derek Middleton, 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 Urology, KFSH&RC, Riyadh, KSA (Discovering Biomarkers for Prostate Cancer – just published results in International Journal Oncology, Jan 2011).
- Department of Medicine, KFSH&RC, Riyadh, KSA (Discovering Markers for Classification of Lupus Nephritis)
- 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 Stem Cell Banking and Discovering Markers for 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**

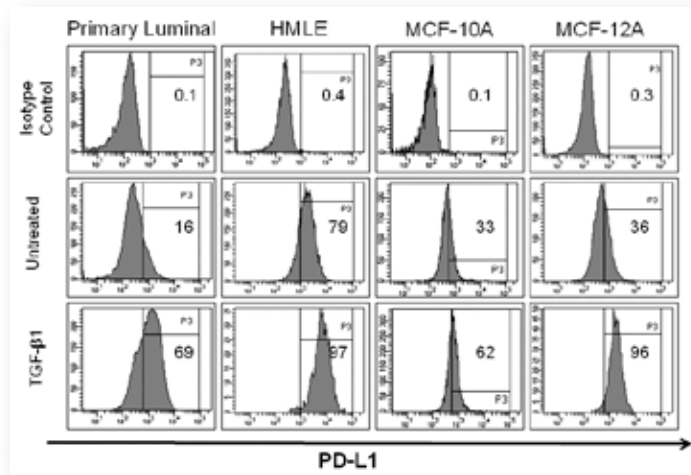
**PROJECT TITLE:** The Role of the Immunomodulatory Molecule B7-H1 (PD-L1) in the Initiation and Maintenance of Cancer Stem Cells. RAC # 2140 001.

**PRINCIPAL INVESTIGATOR:** Dr. Hazem Ghebeh

**CO-INVESTIGATORS:** Dr. Abdullah Alsuliman, Dr. Monther Al-Alwan, Dr. Taher Al-Tweigeri, Dr. Asma Tulbah

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** 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. One of the mechanism by which CSC escape the immune system is by expression of B7-H1. The mechanism of this up-regulation is unknown. In addition, the association of B7-H1 expression and CSC suggest a role for this molecule in CSCs function. In this proposal we will test this hypothesis and we will use different assays to study B7-H1 expression in breast CSCs and the consequence on this expression on CSCs function.

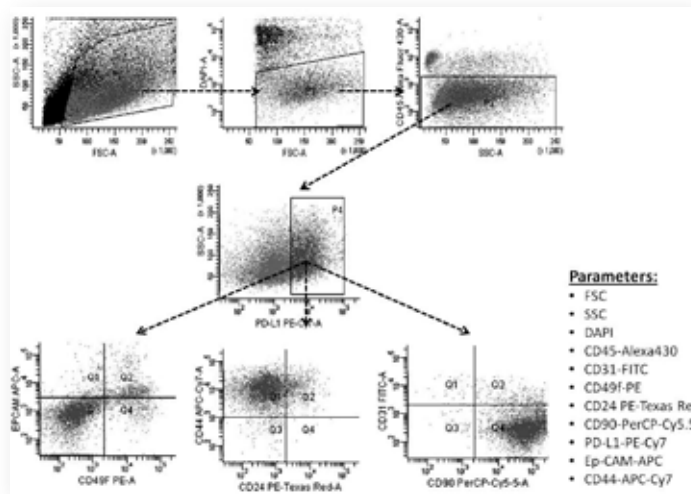
To generate CSCs, we used TGF- $\beta$ 1 to induce epithelial to mesenchymal transition (EMT), a process that is associated with the generation of CSCs. Flow cytometry showed an upregulation of B7-H1 upon EMT induction (Figure 1) explaining the association between CSCs and B7-H1 upregulation.



**Figure 1.** PD-L1 is induced upon epithelial to mesenchymal transition. Flow cytometry histograms for cells before and after continuous treatment with TGF-beta for 2 weeks. Numbers indicates percentage of cells positive for PD-L1.

In addition we were able to use 9-color cell multi-parametric flow cytometry to analyze cells isolated from the normal human breast. Results show that B7-H1 (PD-L1) positive cells were mostly Ep-CAM<sup>high</sup>/CD49<sup>neg</sup>, CD44<sup>high</sup>/CD24<sup>low</sup> and CD90<sup>high</sup>/

CD31<sup>neg</sup>, a typical phenotype of mesenchymal cells. In addition a small population of Ep-CAM<sup>low</sup>/CD49<sup>pos</sup> existed which matches the phenotype of normal breast stem cells were also PD-L1 positive (Figure 2).



**Figure 2.** PD-L1 is expressed in the mesenchymal fraction and possibly the stem/progenitor fraction of human normal breast. Single isolated cell from normal breast tissue obtained from reduction mammoplasty were analyzed with sequential gating. Forward scatter (FSC) and side scatter (SSC) to extract cells from debris. DAPI positive cells were excluded to gate on viable cells only. CD45 were used to exclude hematopoietic cells followed by gating on PD-L1 positive cells. PD-L1 positive cells were further analyzed for Ep-CAM/CD49f, CD44/CD24 and CD90/CD31 expression levels.

**PROJECT TITLE:** Investigating the Role of Cellular Inhibitory Proteins in Eosinophils Apoptosis: Implication in Asthma/Atopy. RAC #2080 026.

**PRINCIPAL INVESTIGATORS:** Dr. Bandar Al-Saud

**CO-PRINCIPAL INVESTIGATOR:** Dr. Chaker Adra

**CO-INVESTIGATORS:** Dr. Ayodele Alaiya, Dr. Monther Al-Alwan, Dr. Hind Al-Humaidan, Dr. Ameerah Gaafar, Dr. Alia Iqniebi

**PROJECT DESCRIPTION:** The observation of delayed eosinophil apoptosis in allergic diseases is a well-established phenomenon. However, the exact mechanism that regulates eosinophil survival in allergy is not fully understood. The aim of this study is to define the role of c-FLIP in apoptosis of eosinophils isolated from individuals suffering allergic reaction compared to control individuals. If c-FLIP plays an important role in the regulation of eosinophils apoptosis, this will add to our understanding of the mechanism of eosinophils role in the development of allergy.

**PROGRESS, MAJOR FINDINGS**

1. This proposal is only recently approved and the required reagents and antibodies have been ordered
2. The optimal PCR conditions have been optimized on the Jurkat cell line, which are positive for c-FLIP
3. Recruitment of asthmatic patients is ongoing

**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

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:**

This study aimed to identify and characterize novel

proteins as biomarkers for normal stem/progenitor cells using expression proteomics approach.

Normal breast tissue was digested and extraction of the mammary epithelial cells was done. Lymphocytes, fibroblast, and endothelial cells were depleted. The isolated epithelial breast cells were FACS sorted. Further enrichment was done by sorting for CD90+ fraction of Ep-CAMlow/CD49f+ cells, and was compared with CD90neg cells. Whole cell lysates of sorted cells were subjected to proteome analysis by 2-DE, MALDI-TOF-MS and LC/MS/MS.

Approximately 190 protein isoforms representing only 90 unique protein species were identified by LC/MS/MS. Only 4 of the 90 proteins are cell surface proteins. Among the identified protein are ABCC6 ATP-binding cassette, sub-family C (CFTR/MRP), member 6, FMS-Related tyrosine kinase 4, Annexin A2, Killer cell lectin-like receptor subfamily C, member 1, Moesin and Neurexin 3.

The results highlight the power of proteomics for discovery of biomarkers for breast cancer stem cells.

Protein patterns in CD90+ and CD90neg fractions of normal breast tissue

We observed high degree of homogeneity in global protein expression profiles from CD90+ and CD90neg cells of the Ep-CAMlow/CD49f+ cells. Figure 1 shows an image of the 2DE-gel electrophoresis of these two populations. Because of very limited sample for analysis (approx 5000 cells), it was not possible to run biological replicates from each analysis groups. However, we managed to identify 2 protein spots that are expressed differently between CD90+ and CD90neg cell populations using 2-DE + MALDI-TOF MS (table 1).

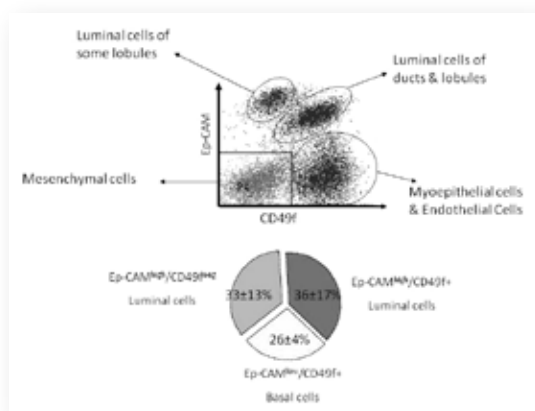
LC/MS/MS protein identification of the Ep-CAMlow/CD49f+ cells

- Due to low protein yield as outlined above, we subjected whole cell lysates of only the

Ep-CAM<sup>low</sup>/CD49<sup>+</sup> cells to LC/MS/MS analysis towards identification of new surface markers at protein level.

- 190 protein isoforms representing only 90 unique protein species were identified by LC/MS/MS.

- Looking for new cell surface protein markers to be used in sorting of these cells while alive, we subjected these 90 identified proteins, to Ingenuity pathway analysis (IPA) for their localization as cell surface proteins. Only 4 of the 90, turned out to be cell surface proteins (Table 1).



**Figure 1.** Flow cytometry work flow: The isolated epithelial breast cells were FACS sorted. Further enrichment was done by sorting for CD90<sup>+</sup> fraction of Ep-CAM<sup>low</sup>/CD49<sup>+</sup> cells, and was compared with CD90<sup>neg</sup> cells.

Accession#	ID Method	Symbol	Entrez Gene Name	Location	Function
O88269	2-DE/ MALDI	*ABCC6	ATP-binding cassette, sub-family C (CFTR/MRP), member 6	Plasma Membrane	Transporter
P35916	2-DE/ MALDI	*FLT4	FMS-Related tyrosine kinase 4	Plasma Membrane	Trans - membrane receptor
Q07936	LC/MS/MS	ANXA2	Annexin A2	Plasma Membrane	
P26715	LC/MS/MS	KLRC1	Killer cell lectin-like receptor subfamily C, member 1	Plasma Membrane	Trans-membrane receptor
P26038	LC/MS/MS	MSN	Moesin	Plasma Membrane	Other
Q9HDB5	LC/MS/MS	NRXN3	Neurexin 3	Plasma Membrane	Transporter

**Table 1.** List of proteins that were differentially expressed between CD90<sup>+</sup> & CD90<sup>-</sup> cells. In asterisks are two of the four proteins spots on 2-DE gels that are uniquely expressed in CD90<sup>+</sup> but absent in CD90<sup>-</sup> cells & identified by MALDI-TOF MS. The rest proteins were identified by tandem mass spectrometry (LC/MS/MS).

**PROJECT TITLE:** Proteomics Approach to Biomarker Discovery in Aplastic Anemia. RAC #2060 021 (Proteomics).

**PRINCIPAL INVESTIGATORS:** Dr. Ayodele Abdulkareem Alaiya and Dr. Mahmoud Al-Jurf

**CO-PRINCIPAL INVESTIGATORS:** Dr. Naeem Chaudhri and Dr. Hazzaa Al Zahrani

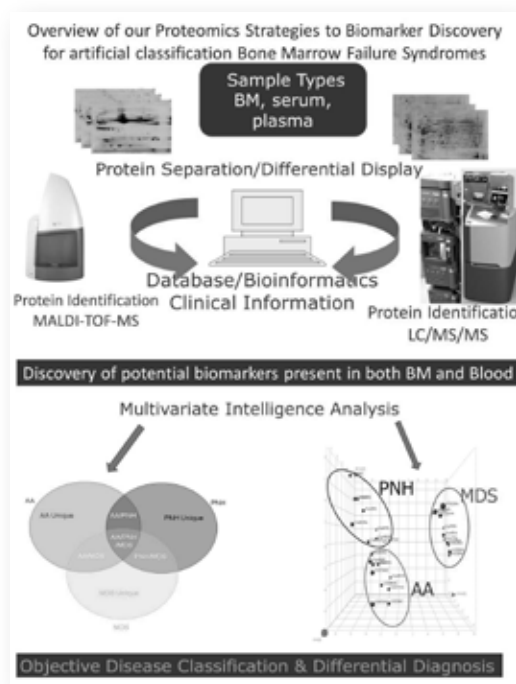
**CO-INVESTIGATORS:** Dr. Mai Al-Mohanna, Dr. Entezam Sahovic, Dr. Fahad Al Mohareb, Dr. Fahad AL Sharif, Dr. Hamad Al Omar, Dr. Ali Al Shanqeeti, Dr. Majed Dasouki

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** Bone marrow failure syndrome is an example of disease entity where accurate diagnosis of Aplastic Anemia (AA), Paroxysmal Nocturnal Hemoglobinuria (PNH) and Hypoplastic Myelodysplastic Syndrome (MDS) is difficult. The aim of this study was to analyze

global protein expression profiles of hematopoietic stem cells derived from bone marrow samples from patients diagnosed with subtypes of bone marrow failure syndromes.

**Experimental Design-** To analyze global protein expression profiles in patients with: Aplastic Anemia, Paroxysmal Nocturnal Hemoglobinuria Myelodysplastic Syndrome, Fanconi Anemia, and normal bone marrow using label free quantitative liquid chromatography /tandem mass spectrometry (LC-MS/MS)

**Goals:** To provide unique capability to identify novel protein biomarkers for differential diagnosis of various bone marrow failure syndromes thus opening the possibility that validated studies can lead to the identification of clinically useful biomarkers.



**Figure 1.** Illustration of our Proteomics Approach to Biomarker Discovery for bone marrow failure syndromes (AA/MDS/PNH) towards artificial classification of bone marrow failure syndromes.



**PROJECT TITLE:** Chronic Myeloid Leukemia: Development and Validation of Therapeutic Hematoproteomic Biomarkers. RAC #2050 040, (Proteomics).

**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, PROGRESS, MAJOR FINDINGS:** Despite advancements in diagnosis and treatment modalities for hematological malignancies, presently, there are no reliable blood tests for disease prognosis or prediction of patient's response to particular treatments. This study aims towards identification

of protein biomarkers for therapeutic response in clinical monitoring of newly diagnosed Chronic Myeloid Leukemia (CML) on Imatinib as first line therapy.

- Experimental Design-To analyze global protein expression profiles of bone marrow and serum samples from 28 chronic-phase CML patients using 2-DE & label free quantitative liquid chromatography /tandem mass spectrometry (LC-MS/MS)
- Goals:
  - To provide unique capability to identify biomarkers entailing less invasive procedures
  - to evaluate for early treatment response and discovery of disease-specific /disease-associated proteins for prognostic monitoring of CML patients.

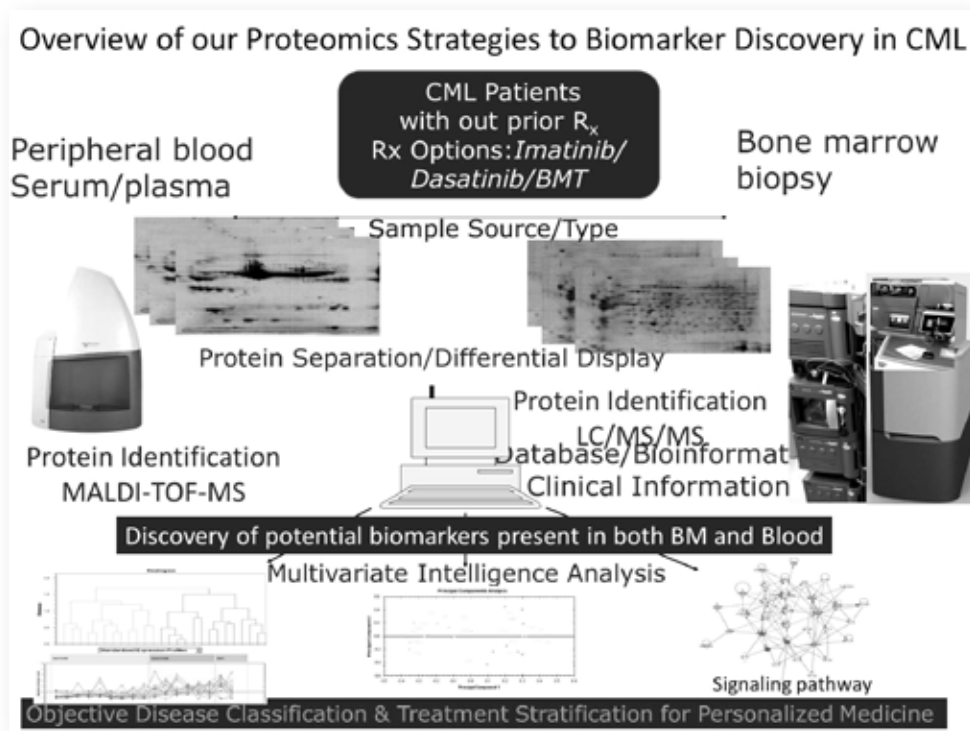


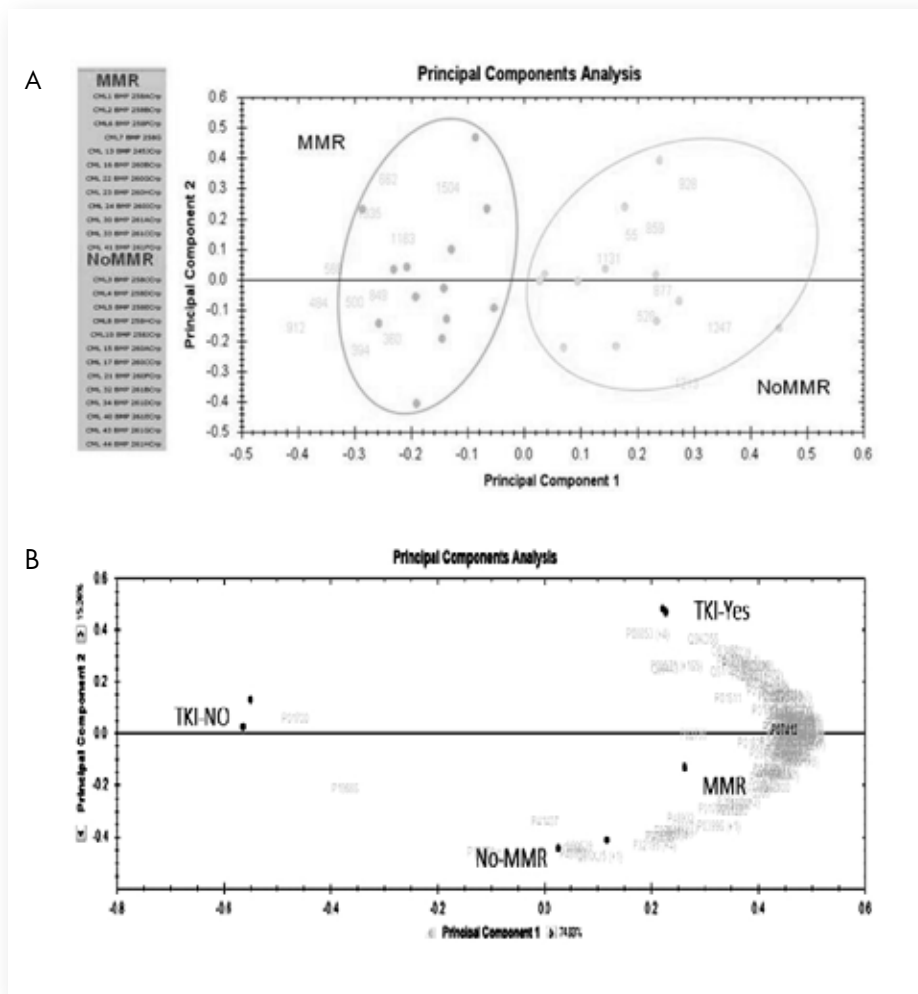
Figure 1. Illustration of our Proteomics Approach to Biomarker Discovery in CML

**LC/MS/MS PROTEIN IDENTIFICATION**

- Samples were evaluated for early Rx response and prediction of Rx options towards personalized medicine
- Sixty three (63) differentially expressed proteins were identified ( $> 2$ -fold change,  $p < 0.05$ ).
- These proteins predicts accurately patients with Major Molecular Response (MMR) vs. No-Major

Molecular Response (NoMMR) at 6 months using unsupervised principal component analysis (Figure 2A & Table 1).

- The panel of proteins also discriminates patients that stays on TKI after 1year of Imatinib Rx from patients ultimately requiring alternative Rx (Figure 2B).



**Figure 2.** Principal Component Analysis using datasets of differentially expressed proteins separated the samples into two groups of MMR and NoMMR (A). The same dataset separates all four sample groups including patients that stay on TKI after 1year of Imatinib Rx from patients ultimately requiring alternative Rx (B). Some the identified proteins were implicated in hematological diseases as potential biomarkers using Ingenuity Pathway Analysis (Table 1).

Accession	Anova (p)	Max fold change	Highest mean condition	Lowest mean condition	Description
P17333	0.0001739	Infinity	MMR-Yes	MMR-No	Napin precursor (1.7S seed storage protein).
P02679	0.0002738	2.51469	MMR-Yes	MMR-No	Fibrinogen gamma chain precursor.
P01611	0.0004346	Infinity	MMR-Yes	MMR-No	Ig kappa chain V-I region Wes.
P08603	0.000505	2.99443	MMR-Yes	MMR-No	Complement factor H precursor (H factor 1).
P44094	0.0006189	Infinity	MMR-Yes	MMR-No	Hypothetical protein HI1014.
Q14624	0.0008244	4.03805	MMR-Yes	MMR-No	Inter-alpha-trypsin inhibitor heavy chain H4 precu
P02787	0.0008246	2.32317	MMR-Yes	MMR-No	Serotransferrin precursor (Siderophilin) (Beta-1-m
P02735	0.0008897	5130	MMR-Yes	MMR-No	Serum amyloid A protein precursor (SAA) [Contains:
Q61147	0.0009327	Infinity	MMR-Yes	MMR-No	Ceruloplasmin precursor (EC 1.16.3.1) (Ferroxidase
P46258	0.0014678	1.99813	MMR-No	MMR-Yes	Actin 3.
Q9KD56	0.0019316	591.324	MMR-Yes	MMR-No	Hypothetical protein BH1363. Complement C3 precursor [Contains: C3A anaphylatox
P12387	0.0019948	1.70652	MMR-Yes	MMR-No	Fibrinogen alpha/alpha-E chain precursor [Contains
P02671	0.002094	3.28658	MMR-Yes	MMR-No	Beta-glucosidase A (EC 3.2.1.21) (Gentiobiase) (Ce
P22073	0.0025276	2.28025	MMR-Yes	MMR-No	Apolipoprotein A-IV precursor (Apo-AIV).
P06727	0.0029126	2.41428	MMR-Yes	MMR-No	Proto-oncogene tyrosine-protein kinase FGR (EC 2.7
P14234	0.0036589	6.37135	MMR-Yes	MMR-No	Putative uracil phosphoribosyltransferase (EC 2.4.
O83462	0.0037936	Infinity	MMR-Yes	MMR-No	Complement C1q subcomponent, B chain precursor.
P02746	0.0039075	2.79378	MMR-Yes	MMR-No	Rhomboid protein (Veinlet protein).
P20350	0.0039176	7.47064	MMR-Yes	MMR-No	

**Table 1.** List of some of identified proteins that were significantly differentially expressed between CML patients with MMR & No-MMR. The proteins were identified by tandem mass spectrometry using Synapt G2 HDMS™ (Waters).

## SUMMARY

- Proteomics holds promise in molecular stratification of CML patients for treatment options.
- We have identified protein signatures capable of prediction of molecular response and choice of therapy for CML patients at 6 months.

Expression proteomics is very promising in personalized medicine, thus opening the possibility that validated studies can lead to the identification of clinically useful biomarkers Future Research Directions

- To validate our findings by including more cases in the study and test whether the observed protein patterns would accurately predict the samples based on their clinical & biological characteristics.
- To extend the analysis to other cytogenetic and clinical responses.

**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 Aljurf

**PROJECT DESCRIPTION:** Despite success in treatment of breast cancer, mortality remains high mainly due to chemo resistance 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:
  - a. Revealing a novel regulator of breast cancer stem cells: implication for targeted therapy. Al Faisal University, Riyadh Saudi Arabia.
  - b. Stem Cells in Health and Disease. Baku World Forum of Young Scientists, Baku, Azerbaijan.
  - c. The role of actin cytoskeleton in the function of Breast cancer stem cells. The 2013 Annual Research Report, Riyadh, Saudi Arabia.
  - d. 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:
  - a. Ghebeh H, Alkhalidi S, Olabi S, Alkhalidi S, Al-Dhfyhan 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:

- a. Revealing a novel regulator of breast cancer stem cells: implication for targeted therapy. Al Faisal University, Riyadh, Saudi Arabia. (invited speaker-November 26, 2014)
  - b. Biology of Stem Cells. Future Scientist Summer Program. King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. (Invited speaker-June, 2014).
  - c. 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 26<sup>th</sup>- 31<sup>st</sup>, 2014)
  - d. The role of actin cytoskeleton in the function of Breast cancer stem cells. The 2013 Annual Research Report, Riyadh, Saudi Arabia (keynotespeaker-April 2<sup>nd</sup>-3<sup>rd</sup>, 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 chemo resistance 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:** Proteomic Analysis, Anti-Resorptive Properties, and Tumor Cell Cytotoxicity of Osteodex in Bone Metastasis from Breast and Prostate Cancer. Proposal # 2080 052 (Proteomics).

**PRINCIPAL INVESTIGATOR:** Dr. Ayodele A. Alaiya

**CO-PRINCIPAL INVESTIGATOR:** Dr. Chaker Adra

**CO-INVESTIGATORS:** Dr. Mai Al-Mohanna, Dr. Andrew Wetzig, Dr. Sten Nilsson, Dr. Marcela Holmberg, Asst Prof. Lennart Meurling, Dr. Raafat El-Sayed, Dr. Falah Al-Mohanna, Dr. Steve Bobis

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** ODX is a novel bi-functional and macromolecular polybisphosphonate developed for treatment of bone metastasis in prostate and breast cancer. High treatment efficacy has previously been demonstrated *in vitro* and *in vivo*. The present study investigates

whether ODX has efficacy also on soft tissue tumor lesions using Expression Proteomics. Twelve female nude mice were injected with approximately 1-1.5 million MDA 231 cells subcutaneously around the mammary pad region. Tumors developed and were allowed to grow until  $\leq 1$ cm before initiating treatment with ODX, administered i.v. 2.5mg/kg, once/week for 5 weeks. Serial measurements of tumor growth during the treatment period were conducted. The animals were sacrificed after 5 doses of ODX and tumor tissues were resected in treated and non-treated animals and histo-pathological evaluation and proteomic analysis were performed. Results: The non-treated mice group developed multiple large size tumors with pronounced ulcerations, while the treated mice showed significantly smaller and less developed tumors without ulcerations (Figures 1&2). The general conditions of the treated mice were much better than the non-treated group. Multivariate analysis of a panel of proteins with significant expression levels unambiguously differs between treatment and no treatment groups, using non-gel based Nano-LC coupled with Synapt G2 (Figure 3). We used label-free MS-based method for comparative protein expression profiling & identified proteins that could be associated with ODX therapy in tumor bearing mice. We identified approximately 300 proteins between treated and non-treated tumor tissues.



**Figure 1.** (A) very small tumors in the treated group compared with (B) massive and ulcerative tumor in the no treatment group. (Also, mice in the treatment group are much physically active than in no treatment mice). All animal experiments were handled and cared for with standard protocols according to Institutional Animal Care and Use Committee policies and guidelines.

Only 16 of these proteins were differentially expressed with significant changes of at least  $\geq 2$ -fold differences between sample groups (Table 2). A data set of the 16 proteins clearly discriminate the sample groups by unsupervised Hierarchical Cluster analysis Figure and principal component analysis (Figure 3 A & B).

**CONCLUSION:** This study using nude mice with breast cancer implants indicate that ODX has very significant treatment efficacy on soft tissue lesions exclusive of its efficacy on bone metastasis. Proteomic analysis results provide a general view of the changes in protein expression profiles after ODX treatment. The data will enable screening for markers to monitor therapy response and to identify proteins associated with the efficacy of ODX therapy.

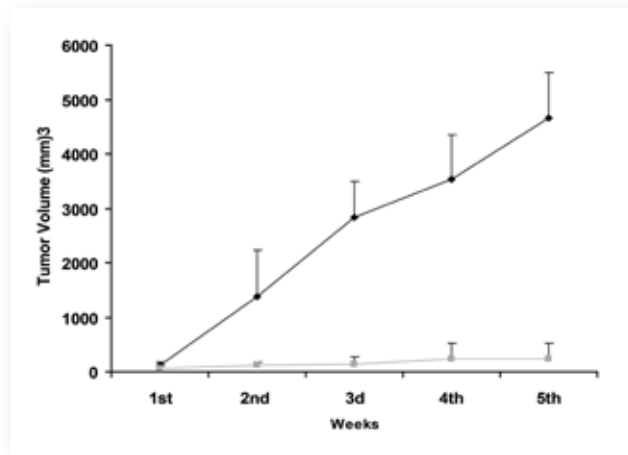


Figure 2. Graph of serial measurements of tumor volume (mm<sup>3</sup>) over treatment duration between tumor bearing treated and un-treated mice (Tumor volume  $V = \frac{1}{2}(\text{width}^2 * \text{length})$ ).

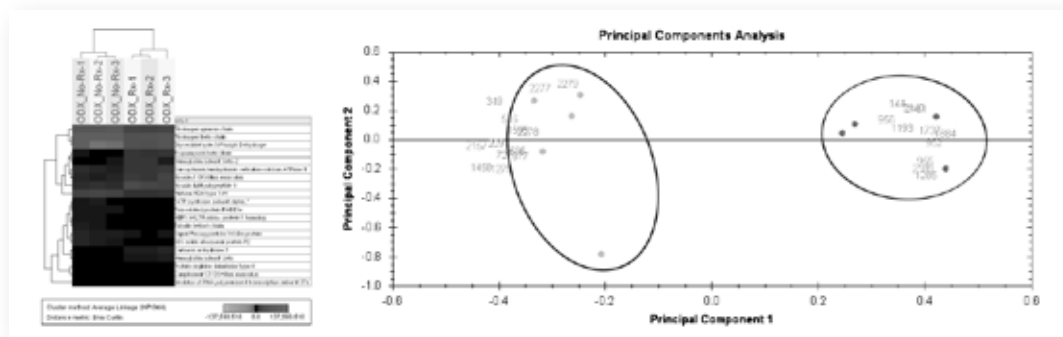


Figure 3. Hierarchical Cluster analysis using the 16 identified proteins with expressively significant change between ODX treated and no treatment tumors. The dendrogram was generated by the J-Express software. (B) Same dataset was subjected to Principal Component Analysis (PCA) and the expression changes allows clear separation into two distinct groups.

Fold Change	ID	Symbol	Entrez Gene Name	Location	Type(s)
2.346	Q8R429	ATP2A1	ATPase, Ca <sup>++</sup> transporting, cardiac muscle, fast twitch 1	Cytoplasm Extracellular	Transporter
7.070	P01027	C3	Complement component 3	Space	Peptidase
5.181	P16015	*CA3	Carbonic anhydrase III, muscle specific	Cytoplasm Extracellular	Enzyme
2.395	Q8K0E8	FGB	Fibrinogen beta chain	Space Extracellular	Other
2.571	Q8VCM7	FGG	Fibrinogen gamma chain	Space	Other
5.870	P02089	Hbb-b2	Hemoglobin, beta adult minor chain	Unknown	Other
2.006	P06467	HBZ	Hemoglobin, zeta	Cytoplasm	Transporter
2.027	Q3TYV2	HHLA1	HERV-H LTR-associating 1	Unknown	Other
3.262	Q5SX40	MYH1	Myosin, heavy chain 1, skeletal muscle, adult	Plasma Membrane	Enzyme
3.219	Q60605	MYL6	Myosin, light chain 6, alkali, smooth muscle and non-muscle	Cytoplasm	Other
1001	Q8K3V4	PADI6	Peptidyl arginine deiminase, type VI	Cytoplasm	Enzyme
5.324	Q9SF91	RAB8B	RAB8B, member RAS oncogene family	Cytoplasm	Enzyme
4.253	P99027	RPLP2	Ribosomal protein, large, P2	Cytoplasm	Other
2.264	P16254	SRP14	Signal recognition particle 14kDa (homologous Alu RNA binding protein)	Cytoplasm	Other
6.511	P58774	TPM2	Tropomyosin 2 (beta)	Cytoplasm	Other
2.337	Q922F4	\$**TUBB6	Tubulin, beta 6 class V	Cytoplasm	Other

**Table 1.** Annotation of Identified proteins with expressively significant change ( $\geq 2$ -fold up or down & p-value of 0.001) between ODX treated and no treatment tumors. (The proteins were identified by LC/MS/MS/Synapt G2 HDMS™ (Waters). Marked in asterisk were proteins that have been already implicated in different drugs that have been approved for treatment of osteoporosis and hormone-refractory prostate cancers.

**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:** Mahmoud Aljurf, Abdelghani Tbakhi, Ameera Gaafar Mohamed, Khaled Al-Hussein

**SIGNIFICANCE AND MAJOR FINDINGS:** Haematopoietic 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- $\gamma$ , TGF- $\beta$ , TNF- $\alpha$ , IL-6 and IL-10. Genotyping was performed by allele-specific polymerase chain reaction (SSP-PCR). The prediction of NK cell all reactivity 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 activating 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.

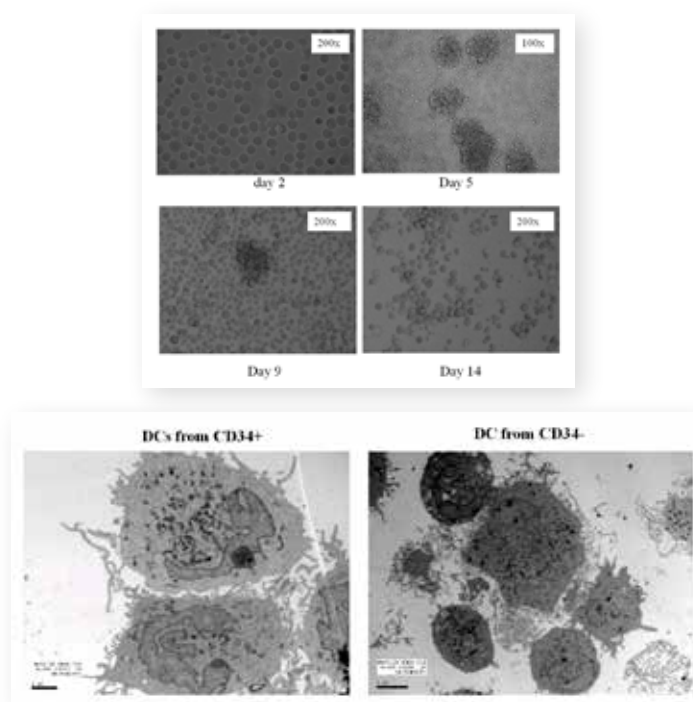
**PROGRESS:** The project was successfully completed and two final reports submitted and accepted by KACST and ORA. Two (2) abstracts were presented nationally and two (2) internationally. One manuscript was published in Transplant Immunology and the 2<sup>nd</sup> is being drafted and will be submitted 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. Iqba, Dr. A. Tbakhi, Dr. Fahad Al-Mohareb, Significance and Major Findings:

**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.



Changes in the morphology of DC from CD34-HPSCs derived from CML patient in 14 days.

**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 counterpart cells 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.

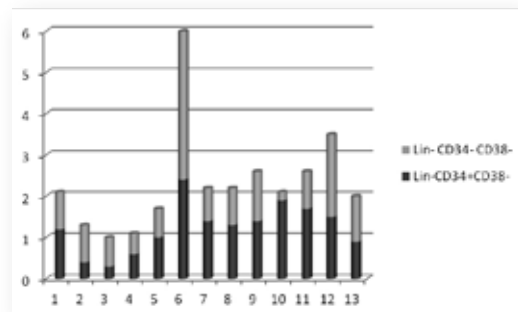
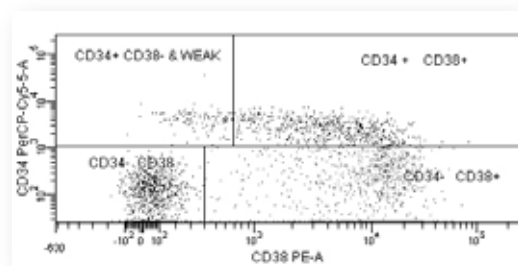
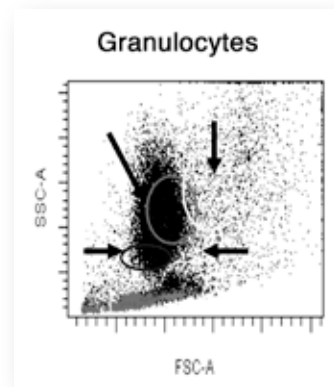
**CONCLUSIONS:** Finally, we examined in this study a novel valuable source (CD34-/lineage-cells) for the generation of human DCs. These DC were found be comparable to DC generated from their counterpart CD34+ as they showed potent functional capacity and hold promises in immunotherapy modality. Further studies exploring capacity of DC generated from CD34-/lineage-cells in the presentation of specific tumor antigens to cytotoxic T cells is warranted.

**PROGRESS:** The project was re-activated on the 11<sup>th</sup> 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

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



% of Primitive hematopoietic stem/progenitor cell stem cells in cord blood samples

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<sup>-</sup>CD34<sup>-</sup>CD38<sup>low/-</sup> and Lin<sup>-</sup>CD34<sup>+</sup>CD38<sup>low/-</sup> 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<sup>-</sup> primitive HSC compartments and hopefully further analysis will facilitate in the discovery of a universal marker(s) and decode the biology of hematopoiesis in health and disease.

A pilot study was performed and the proposal was submitted to KACST.

## 2014 FULL SCIENTIFIC PUBLICATIONS

### PUBLISHED

- 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.
- Alsemari A, Alkhodairy F, Aldakan A, Al-Mohanna M, Bahoush E, Shinwari Z, Alaiya A. The selective cytotoxic anti-cancer properties and proteomic analysis of *Trigonella Foenum-Graecum*. *BMC Complement Altern Med*. 2014 Mar 29;14:114. doi: 10.1186/1472-6882-14-114. PMID: 24679057
- Alaiya A, Fox J, Bobis S, Matic G, Shinwari Z, Barhoush E, Márquez M, Nilsson S, Holmberg AR. Proteomic analysis of soft tissue tumor implants treated with a novel polybisphosphonate. *Cancer Genomics Proteomics*. 2014 Jan-Feb;11(1):39-49. PMID:24633318 [PubMed - indexed for MEDLINE]
- Ghebeh H, Al-Khaldi S, Olabi S, Al-Dhfyhan A, Al-Mohanna F, Barnawi R, Tulbah A, Al-Tweigeri T, Ajarim D, Al-Alwan M. Fascin is involved in the chemotherapeutic resistance of breast cancer cells predominantly via the PI3K/Akt pathway. *Br J Cancer*. 2014 Oct 14;111(8):1552-61. doi: 10.1038/bjc.2014.453. Epub 2014 Aug 12. PMID: 25117814 [PubMed - indexed for MEDLINE]
- Gaafar A, Iqneibi A, Sheereen A, Eldali A, Turpeinen H, Adra C, Al Meshari K, Al Hussein K. Study of the cytokine polymorphisms in correlation to rejection and graft survival in renal allograft donors and recipients from a homogenous Saudi population. *Transpl Immunol*. 2014 Jan; 30(1):34-9. doi:10.1016/j.trim.2013.11.006. PMID: 24316141 [PubMed - in process].

### MANUSCRIPTS IN PREPARATION

- Gaafar A, Al-Omar HM, Manogaran PS, Iqneibi A, F.Al Mohareb, Chaker Adra and Al-Hussein K. Functional and Morphological analysis of DC generated from CD34<sup>+</sup> and CD34<sup>-</sup> hematopoietic precursor of normal donors and CML patients (will be submitted soon).
- Gaafar A, Sheereen A, Iqneibi A, Mohamed G, Al Sulaiman A, Turpeinen H, Al-Mishari K, Al Hussain K. Comprehensive analysis of KIR gene and KIR legend in kidney transplant recipients and their living related donors; association to allograft rejection. (will be submitted soon).
- Gaafar A, Sheereen A, Iqneibi A, Mohamed G, Al Sulaiman A, Turpeinen H, Al-Mishari K, Al

Hussain K. Evaluation of HLA matching by low and high resolution in kidney transplants donors and recipients. (In preparation).

- Sheereen A, Gaafar A, Iqneibi A, Abdelmoneim Eldal, Aljurf M, Al Hussain K. Comprehensive analysis of KIR gene and KIR legend in Haematopoietic Bone Marrow transplant recipients and their living related donors; association to allograft rejection. (In preparation).
- Al-Hussein KA, Rama NR, Abdullah MA, Rozemuller E and Tilanus M. Single Nucleotide Polymorphism G>A at -308 position in TNF-alpha promoter gene is not associated with Type 1 Diabetes in a DR/DQ positive Saudi population (In preparation)

## 2014 ABSTRACTS

### INTERNATIONAL SCIENTIFIC MEETINGS

- Ayodele Alaiya, Naeem Chaudhri, Hafiz Malhan, Tarek Owaidah, Zakia Shinwari, Jonathan Fox, Fahad Alsharif, Said Y. Mohamed, Walid Rasheed, Osman, Ahmed Syed, and Mahmoud Aljurf. Proteomics-Based Approach Predicts Molecular Response and Stratifies Responders to Tyrosine Kinase Inhibitors (TKI) in Chronic Myeloid Leukemia (CML) Patients. 56<sup>th</sup> ASH Annual Meeting & Exposition, 06–09 December 2014, San Francisco, CA, USA.
- Ayodele A. Alaiya. Clinical Cancer Proteomics: Models for Personalized Medicine. 9<sup>th</sup> International Conference of Anti-Cancer Research. 06–10 October 2014, Porto Carras, Sithonia, Greece
- Ayodele Alaiya, Naeem Chaudhri, Tarek Owaidah, Jonathan Fox, Zakia Shinwari, Eman Barhoush, Fahad Alsharif, Said Y. Mohamed, Walid Rasheed, Osman, Ahmed Syed, Feras Alfraih, and Mahmoud Aljurf. Proteomics Analysis Of Hematopoietic Stem Cells For Identification Of Treatment Predictive Biomarkers In Chronic Myeloid Leukemia (CML) Patients, ISSCR, 12<sup>th</sup> Annual Meeting, June 18–21, 2014 at the Vancouver Convention Centre, Vancouver, BC, Canada
- Ayodele Alaiya, Zakia Shinwari, Tarek Owaidah, Fahad Al Mohareb, Fahad Al Sharif, Hazzaa Al Zahrani, Randa Al Nounou, Osman, Ahmed Syed, Naeem Chaudhri and Mahmoud Al Jurf, Molecular Classification Of Bone Marrow Failure Syndrome: Analysis Of Protein Expression Patterns Of Hematopoietic Stem Cells Derived From Plastic Anemia, Hypoplastic Myelodysplastic Syndrome And Paroxysmal Nocturnal Hemoglobinuria Patients ISSCR 12<sup>th</sup> Annual Meeting, June 18–21, 2014 at the Vancouver Convention Centre, Vancouver, BC, Canada.
- Ameera Gaafar, Ayodele Alaiya, Aminah Ghazi Alotaibi, Fatheia Nabil Hamza, Alia Iqneibi, Pulicat Subramanian Manogaran, Amer Al-Mazrou, Iman Barhoush, Morad Ahmed Alkaff, Hind Al-Humaidan, Khalid Al-Hussein. Cellular and Molecular Profiling of Primitive HSC Subsets in Umbilical Cord Blood Samples: Implications for Cellular Therapy. 43<sup>rd</sup> Annual Scientific Meeting ISEH Society for Hematology & Stem Cells. Montreal, Quebec, Canada, 21–24 August 2014
- Ameera Gaafar, Alia Iqneibi, Atia Sheereen, Abdelmoneim Eldali, Hannu Turpeinen, Khalid Al Meshari, Khaled Al Hussein. 6-year Follow-up of Kidney Transplants: Impact of Immunogenetics Factors on Graft Loss. 28<sup>th</sup> European Immunogenetics & Histocompatibility (EFI 2014) Conference, 25–28 June 2014, Stockholm, Sweden.
- Atia Sheereen, Ameera Gaafar, Alia Iqneibi, Abdelmoneim Eldali, Mahmoud Aljurf, Khaled Al Hussein. HLA matched donors with group B KIR haplotypes improve the survival of related hematopoietic stem cell transplantation. 28<sup>th</sup> European Immunogenetics and Histocompatibility (EFI 2014) Conference 25-28 June, 2014. Stockholm, Sweden. Abstract No. P322. Tissue Antigens 77, 370–513 431, 2014).
- Hazem Ghebeh, Abdullah Al-Sulaiman, Hanae Fitwi, Amal Al-Thubaiti, Abdullah Al-Dhfyhan, Asma Tulbah, Taher Al-Tweigeri and Monther Al-Alwan. Epithelial-to-Mesenchymal Transition induce B7-H1 in Breast Cancer Cells. Stem Cell and Cancer Symposium, 01–07 February 2014, Banff Springs, Alberta, Canada

**NATIONAL SCIENTIFIC MEETINGS**

- Ayodele Alaiya, Naeem Chaudhri, Tarek Owaidah, Jonathan Fox, Zakia Shinwari, Eman Barhoush, Fahad Alsharif, Said Y. Mohamed, Walid Rasheed, Osman, Ahmed Syed, Feras Alfraih, and Mahmoud Al-Jurf. Identification of Treatment Predictive Biomarkers in Hematopoietic Stem Cells derived from Chronic Myeloid Leukemia (CML) Patients. Annual Research Report, 16–17 April 2014, Prince Salman Auditorium, KFSH&RC, Riyadh KSA.
- Ameera Gaafar, Ayodele Alaiya, Aminah Ghazi Alotaibi, Fatheia Nabil Hamza, Alia. Iqniebil Pulicat Subramanian Manogaran, Amer Al-Mazrou, Iman Barhoush, Morad Ahmed Alkaff, Hind Al-Humaidan, Khalid Al-Hussein. Cellular and Molecular Profiling of Primitive HSC Subsets in Umbilical Cord Blood samples: Implications for Cellular Therapy. Annual Research Report, 16–17 April 2014, Prince Salman Auditorium, KFSH&RC, Riyadh KSA.
- Ghida Majed Sleiman, Samiyah Alkhaldi, Rayyanah Barnawi, Safiah Olabi, Abdullah Al-Dhfyan, Falah Almohana, Amer Al-Mazrou, Pulicat Manogaran, Hazem Ghebeh, and Monther Al-Alwan. The role of Actin Cytoskeleton in the Function of Breast Cancer Stem Cells. Annual Research Report, 16–17 April 2014, Prince Salman Auditorium, KFSH&RC, Riyadh KSA.
- Abdullah Al-Dhfyan, Ayodele A. Alaiya, Zakia Shinwari, Samyah Al-Khaldi, Falah Al-Mohanna, Asma Tulbah, Monther Al-Alwan, and Hazem Ghebeh. Selective Role of NF- $\kappa$ B induced Chemoresistance in Breast Cancer Stem Cells. Annual Research Report, 16–17 April 2014, Prince Salman Auditorium, KFSH&RC, Riyadh KSA.

**STEM CELL & TISSUE RE-ENGINEERING PROGRAM STAFF****Acting Director**

Ayodele A. Alaiya, MB.BS, PhD

**Administrative Assistant**

Maria Linda R. Macasieb

**Senior Scientist**

Khaled Al-Hussein, PhD Ayodele Alaiya, MB. BS, PhD

**Scientists**

Monther Al-Alwan, PhD Ameer Gaafar Mohamed, PhD Hazem Ghebeh, PhD

**Adjunct/Joint Scientists**

Bandar Al-Saud, MDAida Al-Aqeel, MD, FRCP, FACMG Zikra Al-Khayal, BDS, MS, FABPDMamdouh Al-Baqumi, MD, FASN, FACP

**Post-Doctoral Fellow**

Khaldoon Al-Romaih, PhD Abdullah Al-Suliman, PhD (on scholarship)

**Research Associates**

Manogaran Pulicat, Amer Al-Mazrou

**Research Assistants**

Zakia Shinwari

**Research Technicians**

Abdullah Al-Dhfyhan (In-kingdom scholarship), Eyad Al-Humaidan, Rayyanah Barnawi

**Lab Management Information**

Romeo Caracas

**Graduate Students**

- Kholoud Al-Saud. Obtained M.Sc. (with distinction). The thesis was titled: "Immunological studies of primary cultured breast cancer cell lines isolated from Saudi Patient". The degree was awarded with arrangement with King Saud University, College of Applied Medical Sciences.
- Ghofran Al-Qudaihi. Obtained Ph.D. The thesis was titled: Investigation of M-Phase Phosphoprotein (MPP11) as a novel target for Leukemia T Cell Immunotherapy. The degree was awarded with arrangement with University of Newcastle Upon Tyne, United Kingdom.
- Layla Al-Mansouri. Started her Ph.D. program in Stem Cell & Tissue Re-engineering Program, Research Centre, and now she is presuming the degree in University of Toronto, Canada.

**2013 LIST OF HOSTED STUDENTS/TRAINEES FROM DIFFERENT UNIVERSITIES**

Abdullah Sarkar	Al-Faisal University, Riyadh, KSA
Abrar Al-Fouzan	King Saud University, Riyadh, KSA
Ahmed Hijazi	King Saud University, Riyadh, KSA
Amal Al Thubiti	MRes, Imperial College London, UK
Amer Al Maiman	PhD, University Putra Malaysia
Aminah Al Otaibi	MSc, University of Sussex, UK
Ashwaq Al-Eid	King Saud University, Riyadh, KSA
Dana Al Huzaimi	King Saud University, Riyadh, KSA
Fatmah Abbas Mansour	King Saud University, Riyadh, KSA
Fayza Al Atawi	University of Tabuk, Tabuk, KSA
Gamra Al Qahtani	King Saud University, Riyadh, KSA
Hager Al Seood	King Saud University, Riyadh, KSA
Jawaher Al Sughayyir	MSc, University of Ottawa, Canada
Lamees Al Nabulsi	King Saud University, Riyadh, KSA
Mai Alzaydi	MSc, University of Leeds and Sheffield, England
Manal Yahya	King Saud University, Riyadh, KSA
Manar Al Rashid	King Saud University, Riyadh, KSA
Mayss Al Tahhan	Al Faisal University, Riyadh, KSA
Mohammed Ali Hassan	October University for Modern Sciences & Arts, Egypt
Nada Merghani	King Saud University, Riyadh, KSA
Nouf Al Harbi	King Saud University, Riyadh, KSA
Qais Dirar	Al-Faisal University, Riyadh, KSA
Rawan Al Fraidi	Riyadh College of Dentistry and Pharmacy, Riyadh, KSA
Rawan Al Tassi	Al-Faisal University, Riyadh, KSA
Rawiah Al Ammary	Umm AlQura University, Makkah
Rean Mohammed	MSc, University of Sheffield, UK
Reham Saleem Almatiri	Al Razi Program, RC
Reham Al Obaidan	King Saud University, Riyadh, KSA
Reta Al Onaizan	MSc, University College London, UK
Samiyah Al Khaldi	Umm Al Qura University, Makkah, KSA
Sarah Al Dawood	King Saud University, Riyadh, KSA
Sara Alkusayem	Al Razi Program, RC
Sony Jacob	Pondicherry Institute of Med. Sciences, Ponducherry India
Wadha Bukhari	King Saud University, Riyadh, KSA

**THE MEDICAL AND CLINICAL AFFAIRS 2014  
RESEARCH REPORT**



DEPARTMENT OF  
CRITICAL CARE MEDICINE



## CRITICAL CARE MEDICINE

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**T**he Department of Critical Care Medicine operates a "closed" ICU with 53 beds for adult medical and surgical patients. Annual admissions average 1850. We provide tertiary care facilities for critically ill patients based on evidence-based practices and state-of-the-art technology. Our multidisciplinary medical team consists of 13 consultant intensivists, 14 assistant intensivists, 6 fellows and 8-10 rotating residents. KFSH&RC is the largest transplant center in the area, in our ICU, we take care of patients with solid organ transplant, including liver, lung and kidney in addition to bone marrow transplant. We have an active neurosurgery and oncology surgery dealing with complex surgical cases. Respiratory therapists provide continuous on-site support for patients with acute and chronic respiratory failure, and an experienced multinational nursing staff provides 24-hour cover for all critically ill patients. Critical Care Medicine provides quality care to severely ill patients and working to optimize resource utilization and increase the ability to manage patient needing life support, locally in special lower care areas such as High Dependency Unit or Home Mechanical Ventilation Program, and nationally through the Tele-ICU Program.

**Dr Khalid Maghrabi**  
CHAIRMAN

**Dr Nabil Abouchala**  
DEPUTY CHAIRMAN

ADMINISTRATIVE SUPPORT STAFF

**Alma Llaneta**  
**Ma. Rosario Amao**

### PROTOCOLS IN DEVELOPMENT

Tranexemic acid to reduce transfusion requirements after liver transplantation; Randomized, controlled trial. Investigators: Ghyath Jamil, Mohd, AbouGhanima, Nawal Salahuddin, Dieter Broering

### PROTOCOLS APPROVED BY ORA

1. RAC No. 2141 039. An Algorithm for the Management of Oliguria in Septic Shock (AMOSS STUDY). Investigators: Iqbal Hussain, Nawal Salahuddin, Khalid Maghrabi
2. RAC No. 2141 103. Optic Nerve Sheath Diameter By Bedside Ultrasound is a Reliable Screening Test for Cerebral Edema in the Comatose ICU Patient. Investigators: Nawal Salahuddin, Alaa Mohamed, Nadia Alharbi, , Mini Joseph, Iqbal Hussain, Othman Solaiman
3. Assessing Fluid Status with Vascular Pedicle Width: Relationship with IVC diameter, IVC Variability, & Lung Comet Score; Investigators: Nawal Salahuddin, Iqbal Hussain, Mini Joseph, Hakam Alsaidi, Khalid Maghrabi
4. Estimating the Risks of Organ Failure and Mortality By the PCO<sub>2</sub> Gap in Patients with Shock: A Comparison of Lactate Clearance and  $\Delta$ PCO<sub>2</sub>; Investigators: Mohammad Shaban Raed Kolko Nawal Salahuddin Mohannad AbuRageila. Submitted to ORA for review on 11 January 2015.
5. RAC No. 2131 144. The Intensive Care GLOBal Study on Severe Acute Respiratory Infection (IC-GLOSSARI). Site Investigators: Khalid Maghrabi, Nawal Salahuddin

### STUDIES IN PROCESS

1. An Algorithm for the Management of Oliguria in Septic Shock (AMOSS STUDY). RAC No. Investigators: Iqbal Hussain, Nawal Salahuddin, Khalid Maghrabi
2. Optic Nerve Sheath Diameter By Bedside Ultrasound is a Reliable Screening Test for

Cerebral Edema in the Comatose ICU Patient; Investigators: Nawal Salahuddin, Alaa Mohamed, Nadia Alharbi, , Mini Joseph, Iqbal Hussain, Othman Solaiman

3. Assessing Fluid Status with Vascular Pedicle Width: Relationship with IVC diameter, IVC Variability, & Lung Comet Score; Investigators: Nawal Salahuddin, Iqbal Hussain, Mini Joseph, Hakam Alsaidi, Khalid Maghrabi
4. Estimating the Risks of Organ Failure and Mortality By the PCO<sub>2</sub> Gap in Patients with Shock: A Comparison of Lactate Clearance and  $\Delta$ PCO<sub>2</sub>; Investigators: Mohammad Shaban, Raed Kolko, Nawal Salahuddin, Mohannad AbuRageila

### ABSTRACTS

1. Optic Nerve Sheath Diameter By Bedside Ultrasound is a Reliable Screening Test for Cerebral Edema in the Comatose ICU Patient; Investigators: Nawal Salahuddin, Alaa Mohamed, Nadia Alharbi, , Mini Joseph, Iqbal Hussain, Othman Solaiman. Accepted for presentation at 35<sup>th</sup> International Symposium on Intensive Care and Emergency Medicine, Brussels, March 17 - 20, 2015
2. Assessing Fluid Status with Vascular Pedicle Width: Relationship with IVC diameter, IVC Variability, & Lung Comet Score; Investigators: Nawal Salahuddin, Iqbal Hussain, Mini Joseph, Hakam Alsaidi, Khalid Maghrabi. Accepted for presentation at 35<sup>th</sup> International Symposium on Intensive Care and Emergency Medicine, Brussels, March 17 - 20, 2015
3. Positive fluid Balance is an Independent Risk Factor for Acute Kidney Injury in Critically Ill Patients: Results of a Prospective, Cohort Study. Nawal Salahuddin; Mustafa Sammani; Ammar Hamdan; Mini Joseph; Yasir AlNemary; Rawan Alquaiz; Ranim Dahli; Khalid Maghrabi. Accepted for presentation at 35<sup>th</sup> International Symposium on Intensive Care and Emergency Medicine, Brussels, March 17 - 20, 2015

## PUBLICATIONS

- Tarek Owaidah, Nahlah ALGhasham, Saad ALGhamdi, Dania ALKhafaji, Bandar ALAmro, Mohamed Zeitouni, Fawaz Skaff, Hazzaa ALZahrani, Adher ALSayed, Naser ELKum, Mahmoud Moawad, Ahmed Nasmi, Mohannad Hawari, Khalid Maghrabi. Evaluation of the usefulness of a D dimer test in combination with clinical pretest probability score in the prediction and exclusion of Venous Thromboembolism by medical residents. *Thrombosis Journal* 2014, 12:28.
- Ashraf Nadeem, Nawal Salahuddin, Alyaa ELHazmi, Mini Joseph, Balsam Bohlega, Hend Sallam, Yasser Sheikh, Dieter Broering. Chloride-liberal fluids are associated with acute kidney injury after liver transplantation. *Critical Care* 2014, 18:625.
- N Salahuddin, MG Jamil, J Urresti, M Kherallah. Compliance with the Surviving Sepsis Guidelines: A prospective cohort study of critical care in lesser developed countries. *OA Critical Care* 2014 Jan 18;2(1):1.
- Hakeam A. Hakeam, Mohammed Breakiet, Ayman Azzam,, Ashraf Nadeem, and Tarek Amin. The incidence of cisplatin nephrotoxicity post hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery. *Ren Fail, Early Online*: 1–6. <http://informahealthcare.com/inf>.
- 3 case reports, Ibrahim Sanouri.
- "Positive fluid Balance is an Independent Risk Factor for Acute Kidney Injury in Critically Ill Patients: Results of a Cross-Sectional Study"; Nawal Salahuddin; Mustafa Sammani; Ammar Hamdan; Mini Joseph; Yasir ALNemary; Rawan Alquaiz; Ranim Dahli; Khalid Maghrabi. Submitted to *Critical Care Medicine*; manuscript number: CCMED-D-15-00044.
- Book Chapter: Intracranial Pressure Abnormalities by Othman Solaiman for Neurointensive Care -- update; publishers *Springer*, in press.



DEPARTMENT OF  
FAMILY MEDICINE & POLYCLINICS



## FAMILY MEDICINE & POLYCLINICS

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**T**he Department of Family Medicine & Polyclinics is active in enriching the research activities of the department through its Department Research Committee which provides the academic and administrative support to physicians in the preparation and submission of their proposed research projects. It gives assistance to investigators in a manner consistent with approved policies and procedures of KFSH&RC and as a result there has been an increase in the number of research projects, publications, abstracts and international presentations as compared to previous years. The Committee is comprised of four physicians and two research coordinators.

**Abdullah Alkhenizan, MD**  
CHAIRMAN

### **RAC APPROVED RESEARCH PROJECTS FOR 2014**

**PROJECT TITLE:** The Pharmacoeconomics Picture in Saudi Arabia. (RAC #2141 015).

**PRINCIPAL INVESTIGATOR:** Abdullah Alkhenizan, MD

**OVERVIEW/AIM:**

- To systematically review the current status of pharmacoeconomics in Saudi Arabia including market size and regulatory aspects of pharmaceutical products within the country
- Future analysis of pharmacoeconomics within the country
- To describe the current measures to control health care expenditure and to give practical suggestions to decision makers to curtail the increasing cost of health care services

**PROJECT TITLE:** Verifying Insulin Strategy and Initial Health Outcome Analysis. (RAC #2141 066).

**PRINCIPAL INVESTIGATOR:** Mohammed Alswes, MD

**CO-INVESTIGATORS:** Abdullah Alkhenizan, MD, Hussam Jnaid, MD

Source of funding: Eli Lilly and Company

**OVERVIEW/AIM:**

- To study the proportion of patients with Type 2 Diabetes (T2D), who undergo a significant treatment change within 18 months of initiating insulin injection therapy

### **PLANNED RESEARCH PROJECTS FOR 2015**

**PROJECT TITLE:** Cross-Sectional Study to Correlate the Prevalence of Vertebral Fractures With Bone Mineral Density in a Local Community, and to Identify the Value of Risk Factors and BMD in Predicting Vertebral Fractures

**PRINCIPAL INVESTIGATOR:** Hussain Raef, MD

**CO-INVESTIGATORS:** Muhammad Hammami, MD, K Shaikh, MD, Mohei Aboutaleb, Mohammed Alswes, MD

**PROJECT TITLE:** Human Papilloma (HPV) Viral Load and E6/E7 mRNA Expression as Predictive Markers for the Development of Cervical Carcinoma

**PRINCIPAL INVESTIGATOR:** Fatimah Al Hamlan, MD

**CO-INVESTIGATORS:** Mohammed Al Ahdal, MD, Ahmed Al Qahtani, MD, Tarfah Muammar, MD, Asma Tulbah, MD, Aneela Hussain, MD, Marium Ahmad, MD

**PROJECT TITLE:** A Survey of Flu Vaccine Use and Effectiveness in KFSH&RC.

**PRINCIPAL INVESTIGATORS:** Ibtesam Saleh, MD & Abdelghafour Al Omari, MD

**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 150/4.5mg "as needed" Compared With Pulmicort (Budesonide) Turbuhaler 200mg Twice Daily Plus Turbuhaler 0.4mg "as Needed".

**PRINCIPAL INVESTIGATOR:** Hussam Jnaid, MD

**CO-INVESTIGATORS:** Abdullah Alkhenizan, MD, M Al Bagami, MD

**PROJECT TITLE:** Cancer Control in Gulf Region

**PRINCIPAL INVESTIGATOR:** S Al Othman, MD

**CO-INVESTIGATORS:** A Haoudi, MD, S Alhomoud, MD, Abdullah Alkhenizan, MD, Tawfik Khoja, MD, Al Al-Zahrani, MD

**PROJECT TITLE:** A Pilot Study on the Potential Risk of Brain MRI in Investigating Biochemical Changes in Postpartum Depression.

**PRINCIPAL INVESTIGATOR:** K Alshalali, MD

**CO-INVESTIGATORS:** G Sayed, MD, Patricia McWalter, M, K Alahmadi, MD, M Alruwaili, MD

### SELECTED ACHIEVEMENTS FOR 2014

- Fourteen (14) research projects have been approved by RAC approved since we intensified our Department Research Committee in 2010.
- Two original research projects were accepted for publication in 2014, awaiting confirmation of the date submitted for publication in Osteoporosis International:
  - Knowledge and Use of Folic Acid in a Clinic-based Saudi Pregnant Population (RAC #2111 027) – submitted to SJMMS  
Principal Investigator: Patricia McWalter, MD  
Co-investigator: Alshmassi, Amal, MD
  - Management of Vaginal Penetration Phobia in Arab Women: A Retrospective Study (RAC #2121 047) – submitted to Ann of Saudi Medicine  
Principal Investigator: Tarfah Muammar, MD  
Co-investigator: Patricia McWalter, MD
- Poster/Abstract Presentation of a RAC approved research project
  - A Hussain. "Increasing Trends and Significance of Hypovitaminosis D: A Population-Based Study in the Kingdom of Saudi Arabia". Interdisciplinary Symposium on Osteoporosis 2014, 23-26 Apr 2014, New Orleans, USA.
  - M Shaker. "Increasing Trends and Significance of Hypovitaminosis D: A Population-Based Study in the Kingdom of Saudi Arabia". World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, 2-5 Apr 2014, Seville, Spain

### PUBLICATIONS

- A Hussein. Increasing Trends and Significance of Hypovitaminosis D: A Population-based Study in the Kingdom of Saudi Arabia. Interdisciplinary Symposium on Osteoporosis 2014, 23-26 April 2014, New Orleans, USA.
- McWalter P, Alkhenizan A, Hussain, A. Primary Care Research in Riyadh. *CMAJ Blogs* Nov 2014.
- Alkhenizan A. The Pharmacoeconomics Picture in Saudi Arabia. *Expert Rev Pharmacoecon Outcomes Res.* 2014 Aug;14(4):483-90. Doi: 10.1586/14737167.2014.908712. Epub 2914 Jun 23.
- McWalter, P. Book Review: Great Saves, Great Failures - The Checklist Manifesto: How to Get Things Right. *British Journal of General Practice*, Mar 2014, Vol. 64, No. 620:147.
- P McWalter, T Muammar. Chronic Pelvic Pain of Myofascial Origin in a 53-year-old Patient. (accepted in 2013 by the *Iraqi Journal of Community Medicine* for [ISSN 1684-5382], January 2014)
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- A Hussain, B Cunha, et al. Smallpox. Infectious Diseases book. *Medscape*, Dec 2013 (peer reviewed).
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- 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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- Alkhenizan A, Khoja T. Toward excellence in health care: A call for the Saudi Center for Health Excellence. *JFCM*, 2011;3:99-100.
- Alkhenizan A, Shaw C. Assessment of the accreditation standards of the Central Board for Accreditation of Healthcare Institutions in Saudi Arabia against the principles of the International Society for Quality in Health Care (ISQua). *Annals of Saudi Medicine*, 2010;30(5):386-389.
- P McWalter, A Alshmassi. Swyer-James-Macleod Syndrome in a sixty-year-old patient. *Iraqi Journal of Community Medicine. Index Medicus Eastern Mediterranean Region Journals Directory*, WHO 2010.



# THE DEPARTMENT OF MEDICINE



## MEDICINE

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**T**he Department of Medicine has a robust and productive research activities record. For the last 3 years 73 publications in peer-reviewed journals were accomplished. During the same 3 year period 37 projects were presented at the international meetings. There were 62 research projects submitted and approved by RAC during the last 3 years.

**Hamad AlAshgar, MD**  
CHAIRMAN

The department has had a standing Research Promotion Group (recently transformed into Research Promotion Committee; RPC) for the last 16 consecutive years. It solicits, and conducts a comprehensive peer-review consisting of validation of scientific and ethical integrity prior to the approval. 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. For the last 3 years 41 projects were approved by RPC. This research organ of the department has conducted a formal annual research day for the last 16 years. During the last 3 years, 34, 36, and 35 research projects were presented during 2012, 2013, and 2014 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.

## LIST OF APPROVED RAC PROJECTS (Initiated or ongoing during the year 2014)

**PROJECT TITLE:** Comparing Different Modalities For Dry Weight Evaluation In Dialysis Patients. RAC # 2141075

Source of Funding: KFSH & RC

**PRINCIPAL INVESTIGATOR:** Mohammed Rashwan MD, MRCPI  
**CO-INVESTIGATORS:** Mohammed Mahdi Althaf MD, MRCP(UK), Osman I. Alfurayh MD, Mohammed Said Abdelsalam MD, Shahid Jalil MD, FRCS Ed. A&E (UK), FCEM (SA) Dip PEC (SA)

**ABSTRACT:** Correct assessment of volume status is of paramount importance in establishing dry weight in end-stage renal disease patients on hemodialysis. Currently we rely on clinical assessment with physical examination, chest x-ray and blood pressure management. However, clinical assessment has its limitations and the conclusion on volume status may differ from one physician to the other. Our study aim is to assess physician assessment with two other objective methods - body composition measurement and the utility of bed-side ultrasound to assess the degree of agreement.

**INTRODUCTION:** Volume status is a vital issue in patients undergoing hemodialysis and it is strongly correlated with clinical outcome. A persistent hypervolemic status in dialysis patients will lead to hypertension, left ventricular hypertrophy, that may progress to with congestive heart failure with time. High interdialytic weight gain on top of persistent hypervolemia will further increases the burden for the cardiovascular system.[1] Control of volume state includes fluid and salt restriction, and accurate determination of the dry weight.

Dry weight assessment is a great challenge for nephrologists. Clinically, dry weight is determined as the lowest weight a patient can tolerate without developing intra- or interdialytic symptoms. If this is achieved the patient will be as close as possible

to a normal hydration state without experiencing symptoms indicative of over or under hydration at or after the end of hemodialysis treatment. At dry weight the extracellular fluid volume (ECV) should not be measurably higher than that compared with the healthy population.

Dry weight assessment clinically is not very accurate as some of the fluid may accumulate in the body well before edema becomes clinically evident.[2] For example, dialysis patients with a large interdialytic weight gain, may not have achieved their dry weight, yet still suffer intra-dialytic hypotension for non-volume related reasons, but they come and leave dialysis unit normotensive, and non-edematous, yet remain quite above their true dry weight. In addition patients can have fluid excess in the absence of gross clinical evidence of volume expansion a phenomenon termed "silent overhydration".

Complications of wrong dry weight assessment will lead to either overestimation or under estimation. Overestimation of the dry weight will lead to hypertension; it is well known that around 80% of all hypertension in dialysis patients is due to chronic hypervolemia.[3-5]

In dialysis patients hypertension has been linked to excess cardiovascular and cerebrovascular adverse events which are the most common cause of morbidity and mortality in this population. [6] Chronic hypervolemia also will lead to left ventricular hypertrophy (LVH), which is associated with higher incidence of myocardial infarction,[7] congestive heart failure,[8] and sudden death.[9]

On the other hand under-estimation of the dry weight lead to frequent hypotensive episodes which will lead to patient dissatisfaction with the dialysis prescription, early withdrawal from dialysis, and frequent interrupted sessions, all of which lead to inefficient dialysis, poor nutritional status, and poor outcome.

Many trials have been made looking for different methods to accurately assess patients volume status. [10] The ideal method should be highly sensitive and specific, readily available, inexpensive, fast and easy for use by clinicians, and capable to predict clinical outcomes. Such a method still does not exist. Therefore, more objective and more specific techniques of assessing hydration status have been proposed, each of these having its own advantages and limitations.

These technologies include bioelectrical impedance analysis, biomarkers of volume overload such as natriuretic peptides (B-type natriuretic peptide, BNP), and detection of lung comets by chest US (ULC).

Bioelectrical impedance analysis estimates body composition including total body, extracellular and intracellular water. Body bioimpedance spectroscopy (BIS) is a multi frequency bioimpedance [8, 9]. BNP is a peptide synthesized and stored in

**SPECIFIC AIM:** To determine if bed-side US and body composition measurement are useful adjuncts to dry weight assessment in addition to physician clinical assessment.

**PROJECT TITLE:** A Report Of Arterio-Venous Access Created In The Arm With Ipsilateral Central Venous Occlusive Disease In Hemodialysis Patients - Case Series. RAC # 2141028

Source of Funding: KFSH& RC

**PRINCIPAL INVESTIGATORS:** Naveed UlHaq MD, FASN

**CO-INVESTIGATORS:** Mohammed Mahdi Althaf MD, MRCP(UK), Osman M. Alfurayh MD

**ABSTRACT:** Central venous occlusive disease (CVOD) is common in hemodialysis (HD) patients; most often secondary to prior central venous catheterization. CVOD usually impedes creation of arterio-venous (AV) creation in the ipsilateral arm. We want to report outcomes of a series of HD patients with CVOD in addition to multiple exhausted sites of AV

access who underwent AV access creation in the ipsilateral arm as a last resort in at our institution since Jan 2008 to date.

**INTRODUCTION:** The number of patients requiring hemodialysis is increasing. Vascular access is central to patients with end-stage renal disease who require renal replacement therapy in the form of hemodialysis. With appropriate chronic kidney disease management, it is recommended that patients are referred for vein mapping and appropriate access creation in the form of an arterio-venous fistula (AVF) or arterio-venous graft (AVG) prior to the need for initiating dialysis. This is done in the hope to avoid patients initiating dialysis through a central venous catheter, which are associated with much more morbidity and mortality. For patients who develop central venous stenosis it is currently recommended to avoid creating an AVF or AVG in the ipsilateral limb, thus exposing them to the risk of dialysing through a CVC. In the past few years we have been creating AV access in patients with ipsilateral CVOD as a last option.

#### **SPECIFIC AIMS**

- To report the success of AV access created in the ipsilateral limb with central venous stenosis.
- Assess and report the primary and secondary patency of such an access.
- Assess and report the number of interventional procedures required to maintain such an access
- Assess and report the access flow and life of these AV access

**PROJECT TITLE:** Vascular Access Types In Patients Starting Hernodialysis With Failed Kidney Transplants: A Retrospective Analysis. RAC # 2131090.

Source of Funding: KFSH& RC

**AUTHORS:** Naveed UI Haq, MD, FASN, Mohammed Mahdi Althaf MD, MRCP(UK), Mamdouh Albaqumi, MD, FASN, Hassan Aleid, MD, Khalid Abdul M. Alrneshari, MD, Lutfi Alkorbi, MD.

**ABSTRACT:** Native arteriovenous fistulae (AVF) are the preferred while central venous catheters (CVC) are the least preferred vascular access in patients with end stage renal disease (ESRD) requiring hemodialysis (HD). Patients with CVC as vascular access for HD have poor outcomes on HD as compared to patients who have AVF. Despite this, about 80% of the patients who reach ESRD start HD with a CVC. One of the factors thought to be responsible for low AVF and high CVC rates at the initiation of dialysis is late referral of these patients to a nephrologist in the course of chronic kidney disease (CKD). This late referral does not leave enough time for nephrologist to plan adequately for dialysis thus leading to high prevalence of CVC rather than AVF. AVF needs time to create and mature to be used for HD. To test the validity of this hypothesis, we plan to retrospectively analyze the type of vascular access at the time of initiation of HD in renal transplant patients who subsequently failed their renal allograft leading to HD. These patients classically have close follow up by nephrologist, and if the early referral hypothesis is correct, should have a higher prevalence of AVF at the time of initiation of HD post renal allograft failure.

**INTRODUCTION:** Hemodialysis (HD) vascular access dysfunction is a huge clinical problem which results in significant clinical morbidity in patients with ESRD, causing a severe economic burden on any health care system. AVF is the preferred form of permanent dialysis access as it is associated with the best long term outcome as compared to other forms of dialysis access especially CVC.

Despite the clinical benefits, many patients on HD do not have AVF as their vascular access and as much as 80% of patients start hemodialysis with a CVC. There are currently about 13000 patients with ESRD on dialysis in the kingdom and it is rising at a rate of about 5-7%/year according to the statistics provided by Saudi Center for Organ. One of the reasons thought to be responsible for low AVF rates is late referral of the patients with CKD to the nephrologist. This does not leave enough time for

the nephrologist to plan renal replacement therapy (RRT) on these patients before they develop ESRD. As a result HD is started without proper planning leading to higher use of CVC, which can be inserted and used immediately for dialysis. AVF on the other hand needs time for creation and proper maturation before it can be used for dialysis. To test the hypothesis that late referral is the primary cause of poor AVF rates at the start of dialysis we would like to retrospectively analyze the vascular access type at initiation of dialysis in patients who received renal transplantation and subsequently their renal allografts failed. These patients are closely followed by nephrologists and as such should have a higher rate of AVF at dialysis start if the hypothesis of late referral is correct.

**AIM:** To assess the vascular access type and planning for dialysis at the start of dialysis in patients who fail their renal allografts and are closely followed by nephrologist.

**PROJECT TITLE:** Assessing Clinical Utility Of The Criteria For Accessory Vein Obliteration For Failing Arteriovenous Fistulae. CAVO Trial. RAC # 2141 125.

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

**PRINCIPAL INVESTIGATOR:** Naveed Haq MD, FASN

**CO-INVESTIGATORS:** Mamdouh Albaqumi, MD, FASN, Edward Bentz Devo, PhD.

**BACKGROUND:** Hemodialysis (HD) vascular access dysfunction is a huge clinical problem which results in significant morbidity amongst patients with End Stage Renal Disease (ESRD), causing a severe economic burden on any health care system. Native arteriovenous fistula (AVF) long term outcome as compared to other forms of dialysis access. Despite the clinical benefits, many patients on HD do not have AVF as their dialysis access. One of the reasons for low AVF rates is early fistula failure (EFF)'. EFF is defined as an AVF that never

develops adequately for dialysis (failure to mature) or which fails within 3 months of starting dialysis<sup>8</sup>. An adequate AVF for dialysis according to Dialysis Outcome Quality Initiative (DOQI) guidelines is the one which a.) has a flow of greater than 600ml/min, b.) has a diameter of 0.6cm or greater and c.) is approximately not deeper than 0.6cm from the skin surface. Between 23%–46% of newly constructed AVF have problems with early failure resulting in a dismal one year patency of 60-65%<sup>6</sup>. In order to devise a strategy to prevent EFF, one needs to understand the physiology of fistula maturation. Creation of an AVF leads to an immediate increase in flow through the vein due to the pressure gradient created<sup>1</sup>. This increase in flow leads to increase wall shear stress which is defined mathematically by the formula  $4\eta l v n r^3$ , where  $\eta$  is blood viscosity,  $Q$  is blood flow and  $r$  is vessel radius<sup>14</sup>. Shear stress thus is directly proportional to blood flow while inversely proportional to vessel diameter. After the creation of the AVF, the flow mediated increase in shear stress is mitigated by vessel dilatation through biological mediators<sup>15</sup>.

Consequently the shear stress is brought back to pre-anastomosis levels leading to vessel dilation. It seems that this positive remodeling of the vein leading to AVF maturation is dependent on increase in blood flow rather than the increase in pressure<sup>16</sup>. Any pathology affecting the blood flow through the newly constructed AVF can thus lead to failure to mature.

The two most important causes for EFF amenable to intervention are stenosis anywhere in the circuit and/or presence of accessory veins. While stenosis development is pathological and accessory vein (av) presence is natural, both lead to decreased blood flow through the main AVF circuit, which may be responsible for failure to mature. Addressing these two entities in a timely fashion can lead to salvage of many AVF, which otherwise would have been abandoned. Although management of stenosis is well established with relatively clear guidelines, the management of av lacks clear scientific approach. It

has been anecdotally recommended that any av with a diameter greater than 25% of the AVF diameter should be considered for ligation. It is also suggested that the significance of an av can be ascertained by assessing the flow of contrast through the av during an angiogram or by assessing the augmentation of AVF after manually occluding the av during the procedure<sup>22</sup>. These current recommendations are very subjective and none have been adequately studied to date leading to considerable debate on the issue of when to obliterate an av. A scientific approach to obliteration of av is essential to avoid an unnecessary procedure, which may even be harmful. Also, obliterating a non-significant av and waiting for AVF to mature may cause a delay in making a definite decision for the patient. These patients may have other factors and not av as the cause of EFF. Conversely, not obliterating a significant av may also delay the use of AVF for dialysis by causing EFF. In a recent study we recommended a hemodialysis arteriovenous flow quantification-diameter (HAQ) criteria for accessory vein obliteration. The HAQ criteria for av obliteration is based on computational flow dynamic (CFD) models of AVF created using 2 dimensional CFD software. This criteria has not been tested in clinical trials and its clinical utility has not been established to date. The purpose of this randomized, controlled, blinded, prospective trial is to assess the clinical utility of the HAQ criteria as compared to current recommendations for av obliteration.

**SPECIFIC AIM:** The purpose of this randomized, controlled, blinded, prospective trial is to assess the clinical utility of the HAQ criteria as compared to current recommendations for av obliteration.

**PROJECT TITLE:** The Protocol for the Study of Efficacy and Safety of Rituximab in the Treatment of Resistant Glomerulonephritis. RAC # 2141 041

Source of funding: KFSH& RC

**PRINCIPAL INVESTIGATOR:** Maged Hussein, MBBCh, FACP, FASN

**CO-INVESTIGATORS:** Abdulrahman Alkhan, MD

**INTRODUCTION:** The nephrotic syndrome is an important cause of chronic kidney disease (CKD) that may progress to end-stage renal disease (ESRD). The treatment of the different glomerulonephritides (GN) is still not satisfactory and quest for novel treatments for GN continues especially for the resistant cases, since progression to ESRD is still inevitable in most of them.

Biologic injectable drugs that neutralize B-lymphocytes such as the chimeric anti- CD 20 (Rituximab) have been proven efficacious in the treatment of non-Hodgkin's lymphoma, rheumatoid arthritis, auto immune hemolytic anemia, and renal transplantation. These medications may induce remission of immune mediated GN such as membranous, IgA, focal segmental GN, lupus nephritis, and vasculitis.

The research in the Saudi Arabia has been mostly epidemiological and restricted to the patterns of the GN in it. Study of rituximab's efficacy and side effects in the treatment of GN may be warranted due to the promising effects from previous studies. This may accomplish the aim of the strategies of the preventive medicine for saving the native kidneys by seeking kidney rescue therapies instead of the expenditure on the expensive dialysis and transplantation, or save the transplanted kidney in case of recurrent GN after kidney transplantation.

**AIM OF THE STUDY:** To determine the efficacy and safety of rituximab as a kidney rescue therapy for the different types of glomerulonephritis causing refractory nephrotic syndrome in order to prevent progression of renal failure.

**PROJECT TITLE:** The Renal Response to Therapeutic Plasma Exchange in Rheumatic Disease: Relation between Short and Long Term Outcome. RAC # 2141042.

Source of Funding: KFSH & RC

**PRINCIPAL INVESTIGATOR:** Ahmed Shaikh

**CO-INVESTIGATORS:** Hanan Al Hamzi<sup>1</sup>, Walter Conca<sup>1</sup>, Hind Al Humaidan<sup>2</sup>, Abdullah N. Al Dalaan<sup>1</sup>, Ali Al Rehaily<sup>1</sup>, Salman S. Al Saleh<sup>1</sup>

**BACKGROUND:** Therapeutic plasma exchanges (TPE) have been used in the management of various autoimmune and connective tissue disorders with variable results regarding its benefit and long term outcome. However, the relation between the short and long term is not clear. To the best of our knowledge, this is the first study to highlight this relationship.

**AIMS:** In this study we aimed to see if the renal short term outcome can predict the long term outcome, that it can help in putting the management and follow up plan for these patients.

**STUDY DESIGN:** Longitudinal retrospective observational single centre study by doing chart review for all patients who underwent TPE for renal involvement. Looking for disease status and renal response in the form of complete, partial and no response one month post TPE and to be compared to the long term outcome at 2 years.

**INTRODUCTION:** Therapeutic plasma exchange (TPE) is a process by which large volume of plasma is removed and replaced with replacement fluid leading to removal of large molecular weight substance. In rheumatic disease TPE have been used for many years in the management of multiple auto- antibodies mediated diseases. It has been found to be beneficial for those patients with severe immune complex mediated renal disease who required dialysis. The long term outcome of this intervention have been studied. However the relation between the short and long term outcome have been not addressed. In this study we aim to see if the knowing short term response after TPE can predict the long term outcome, which can help in the follow up and management.

In some studies TPE have been shown to be not significantly different than conventional therapy in patients with mild and severe systemic lupus erythematosus (SLE).

On the other hand, treatment with TPE for 2 years, had been associated better preservation of the renal renal function, reduced disease activity, fewer admissions to hospital and less need for corticosteroids and immunosuppressive therapy. In addition to that, the use of cyclosporine A and TPE resulted in quicker resolution of symptoms (arthralgia and serositis) and decreased doses of cytotoxic drugs. In addition to removal of pathogenic autoantibodies, TPE have been found to have an effect on the peripheral level of T regulatory cells that significantly increased during the course of TPE. The increased number of T regulatory was accompanied by a decrease in the disease activity as measured by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), which may be related to elimination of interferon alpha and lymphocytotoxic antibodies.

The study of 41 patients with ANCA-associated vasculitis patients requiring dialysis at Presentation, who were treated with plasma exchange, corticosteroids, and intravenous cyclophosphamide showed that at 3 months, 7.3% patients had died on dialysis, 29.3% remained dialysis dependent, and 63.4% were dialysis independent. Four patients subsequently reached ESRD at a median time of 83 days. Thirty-seven (90%) patients reached 1 year follow-up, 13 (35%) remained dialysis dependent, and 24 (65%) had independent renal function TPE have been shown to be superior to methylprednisolone in preventing dialysis at 3 months in patient with ANCA associated vasculitidies presenting renal insufficiency characterized by creatinemia  $\geq$  500 micro mol/L.

TPE was associated with a reduction in risk for progression to ESRD of 22% at 3 months and 24% at 12 months in patients treated with TPE in comparison to intravenous methylprednisolone

group. However, there was no significant difference in mortality between the two groups.

Recently they found that additional plasmapheresis for 26 patients with antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) with progressive disease despite treatment with cyclophosphamide and steroids had lead to significant improvement in renal function with similar long-term outcome in both renal and patient survival when compared with 50 matched-disease controls.

The co-existence of pulmonary hemorrhage with renal disease have been found to carry very high mortality up to 50%, in these situation the combination of immunosuppressive therapy and plasmapheresis may be life-saving.

Adverse event rate of TPE like hypotension, electrolyte abnormalities, bleeding, infection and anaphylactic have been ranging between 5-11 %. The overall incidence of death is 0.03 to 0.05 %.

#### **OBJECTIVES:**

##### **Primary:**

- To determine the relation between renal response at 1 month and 2 years post TPE

##### **Secondary: To look for:**

- Mortality
- Adverse events related to TPE
- Factors affecting response to TPE
- To determine the relation between renal response at 6 months and 2 years post TPE
- To observe the relation between early response post TPE and the response to cyclophosphamide at 6 months

**PROJECT TITLE: An International Multicenter Prospective Observational Study to Evaluate the Epidemiology, Humanistic & Economic outcomes of Treatment for Chronic Hepatitis C Virus (HCV). RAC# 2141 076**

Source of Funding: Abbvie

**PRINCIPAL INVESTIGATOR:** Mohammed Khan, MD

### **Epidemiology**

Hepatitis C virus (HCV) infection is a public health problem throughout the world. It is estimated that approximately 130-210 million individuals are chronically infected with HCV<sup>1</sup>. The prevalence varies markedly from one geographic area to another. There are six major genotypes of HCV (and a large number of subtypes), and the distribution of these varies globally. Genotypes 1 through 3 are found worldwide; genotype 4 is found predominantly in the Middle East, central Africa, and Egypt; genotype 5 in South Africa; and genotypes 6 through 11 in Asia (Figure 1). HCV genotypes 1a and 1b are the most common forms, accounting for 60% of HCV infection

### **Natural History of HCV Infection**

HCV is transmitted by parenteral exposures to contaminated blood: injection drugs use (IDU), exposures in health-care settings, inadequate infection-control practices (tattoo, piercing). Transmission rarely follows receipt of blood, tissues, and organs from HCV infected donors who were not identified during routine screening activities, which have been mandated in most countries since 1992. Occupational, perinatal and sexual exposure also can result in transmission of HCV.

Around 80% of individuals exposed to HCV do not clear the virus. Chronic infection can lead to progressive liver disease. 3-11% of those chronically infected will develop liver cirrhosis within 20 years with associated risk of liver failure and hepatocellular carcinoma (HCC). Known factors for the progression of liver disease are: duration of HCV infection, male gender, excessive alcohol consumption, coinfection with HIV and hepatitis B virus (HBV), concomitant steatosis, obesity. Infection with hepatitis C virus is linked to the development of insulin resistance (IR) and type 2 diabetes (DM). It is proved also that presence of DM and IR may accelerate progression of liver disease in patients infected with HCV. Finally, HCV-infected patients

with IR and DM seem to have poorer response to anti-HCV regimen. Complications of chronic HCV infection include also a wide spectrum of generalized extrahepatic disease manifestations, which increase significantly morbidity and mortality. The comorbid conditions impact HCV treatment eligibility, tolerability and efficacy.

### **Treatment of HCV**

The main treatment objective is to cure HCV through a sustained elimination of the virus, thereby, preventing serious liver related complications and death. It is difficult to define response to treatment by a clinical endpoint due to the slow progression of chronic HCV infection over multiple decades.<sup>1,5</sup> Because of this, surrogate virological parameters are used to define treatment response. Of the several virological responses that may occur, the sustained virological response (SVR) is the most critical, defined as the absence of serum HCV ribonucleic acid (RNA) by polymerase chain reaction (PCR) assay, 24 weeks following therapy completion.<sup>1</sup> Individuals treated for HCV that achieve a SVR are considered cured. Other notable virological responses include an early virological response (EVR; defined as HCV RNA negative or 22 log decline in HCV RNA at week 12 of treatment) and a rapid viral response (RVR; defined as HCV RNA negative at week 4 of treatment).

The current on market treatment for HCV infection is a combination of pegylated interferon alfa (Peg-IFN) and ribavirin (RBV). However, use of these medications can be associated with the development of side effects that can significantly impact health-related quality-of-life (HRQoL). Clinical trials found treatment with Peg-IFN and RBV to be curative in approximately 54% to 63% of individuals with HCV however, SVR rates vary substantially by HCV genotype, HCV treatment history and ethnicity. Individuals infected with genotypes 2, 3 and 6 typically respond more favorably to Peg-IFN plus RBV, while individuals with genotype 1, 4 and 5 have poorer response. A SVR is harder to achieve in individuals with HCV genotype 1 compared with

other genotypes; therefore, the treatment regimen for genotype 1 usually involves longer period of time to obtain a higher rate of SVR. Additionally, direct acting antivirals (DAAs), specifically the protease inhibitors boceprevir and telaprevir, have recently been approved by the Food and Drug Administration and the European Medicines Agency for treatment of HCV genotype 1 in combination with Peg-IFN and RBV. This combination therapy has significantly improved treatment effectiveness with rates of SVR reported as high as 75% among treatment-naïve HCV genotype 1 individual. The limitations of currently approved and recommended triple therapy are: significant increase in pill burden, worsening of tolerability, additional DAA-specific adverse effects like rash, pruritus, dysgeusia, increased cost and continuous need for interferon use

#### STUDY OBJECTIVES

##### Phase 1:

- To describe the epidemiology of patients seeking care for HCV

##### Phase 2 and 3:

- To determine how HRQoL values at baseline and changes from baseline may affect treatment completion of IFN-containing therapy for HCV infection
- To assess the impact of HCV and HCV treatment on work productivity and activities of daily living
- To estimate resource utilization associated with HCV treatment
- This is an epidemiological observational study. Therefore it is not designed to identify or
- Quantify a safety hazard relating to an authorized medicinal product.

**PROJECT TITLE:** Video Capsule Endoscopy in Clinical Practice at KFSH&RC (A Retrospective Chart Review). RAC 2141 078.

Source of Funding: KFSH& RC

**PRINCIPAL INVESTIGATOR:** Feras Jemeeli, MD, Mohammed Khan, MD

**CO-INVESTIGATORS:** Al Ashgar, Hamad Ibrahim MD, Al Quaiz Mohammed Nahedh MD, Al Sohaibani Fahad MD, Al Fadda Abdulrahman MD, Aymen Al Muhaidb MD, Alotay, Abdulwahed MD. M. Shoukri MD, Adnan Almahrouq.

**ABSTRACT:** Video capsule endoscopy (VCE) is a powerful diagnostic tool that has proven especially useful in imaging the small intestine. VCE technology offers greater magnification than traditional endoscopy while also providing excellent resolution. It is a clinically useful tool for detecting occult bleeding and superficial lesions that are not radiographically observed; it may also provide functional information as the capsule moves passively through the small intestine. VCE has been favorably compared with push endoscopy in patients with obscure GI bleeding VCE appears to have a clinically relevant positive impact on patient treatment and outcome. In this proposed study, we aim to evaluate its role as a diagnostic tool for a number of gastrointestinal diseases as well as its possible complications. Study findings may be used as parameters that would aid in the design of possible future prospective studies. We aim to perform a retrospective chart review on 303 patients who had undergone capsule endoscopy in King Faisal Specialist Hospital and Research Center. We aim to collect the demographic data, indication, prior diagnostic tests, capsule findings and interventions following VCE. All Data shall be collected in a data collection sheets then to be processed by Statistical Package for the Social Sciences (SPSS) software.

**BACKGROUND:** Video capsule endoscopy (VCE) is a powerful diagnostic tool that has proven especially useful in imaging the small intestine. VCE technology offers greater magnification than traditional endoscopy while also providing excellent resolution. It is a clinically useful tool for detecting occult bleeding and superficial lesions that are not radiographically observed; it may also provide functional information as the capsule

moves passively through the small intestine. The development of endoscopy enabled direct visualization of the esophagus, stomach, proximal small bowel, and colon. However, even with these technological advances, certain limitations remained in the noninvasive diagnosis of gastrointestinal (GI) tract pathology. Much of the small bowel is not accessible with traditional endoscopy or even push endoscopy (which allows imaging up to 80-120 cm beyond the ligament of Treitz) but can be visualized with the capsule endoscope. Capsule endoscopy is superior to radiographic techniques in the detection of mucosal disease and angiodysplasia. Investigators have capitalized on the advantages of this approach, revealing an expanding list of clinical indications. Technical advances in many areas (eg, optical design, light-emitting electrodes, and image sensors) were essential to the development of VCE, and the design was completed in 1997. In 1999, the first volunteer studies were performed, and high-quality images from volunteers were published in the literature shortly thereafter. In 2001, VCE was approved by the US Food and Drug Administration (FDA) for use in patients in the United States, and by 2003, the capsule endoscope had already been used in more than 4000 patients. VCE has primarily been used as a diagnostic tool for detecting obscure GI bleeding, but it has also aided in the diagnosis of inflammatory bowel disease (IBD) and celiac disease and helped in the detection of small bowel neoplasia. GI bleeding is obscure when it continues or recurs after upper and lower endoscopic examinations have found no source. Most obscure GI bleeding is due to lesions in the small intestine, a region that has traditionally been difficult to image adequately. Before VCE, the standard procedure comprised a combination of diagnostic methods, including upper endoscopy, colonoscopy, and push endoscopy, as well as enterolysis, nuclear bleeding scans, angiography, and small-bowel follow-through studies. VCE, which visualizes the entire mucosa of the small intestine, allows a more complete exploration. Capsule endoscopy may detect superficial lesions that barium studies miss. VCE has proven safe and effective and has a high

diagnostic yield. The diagnostic yield is greatest if the examination is performed within 1 month of the bleeding episode. Both of the major forms of IBD (ie, Crohn disease and ulcerative colitis) may involve the colon, but they may often be distinguished from each other on the basis of upper GI tract involvement. Proper diagnosis informs treatment decisions, such as electing to pursue surgical rather than aggressive medical management for treatment-refractory individuals. Crohn disease affects the small bowel in most individuals; in 30% of patients, the disease is limited to the terminal ileum. The traditional approach to this diagnosis involves esophagogastroduodenoscopy, ileocolonoscopy, and radiography; unlike capsule endoscopy, these studies are limited in their ability to assess the jejunum and the proximal ileum. Barium studies are not as sensitive for the detection of early lesions, and traditional endoscopy is limited to the distal and proximal bowel. When used to evaluate IBD, capsule endoscopy allows visualization of lesions (eg, small bowel erosions and ulcerations) in areas that other forms of endoscopy or radiography would not visualize. Capsule endoscopy can localize and define the extent and activity of IBD. Small bowel neoplasia occurs in 75% of patients with Peutz-Jeghers syndrome (PJS) and 90% of patients with familial adenomatous polyposis (FAP). In patients with FAP, therapeutic interventions in jejunal and ileal polyps remain undefined, perhaps because of the low incidence of nonduodenal small-bowel cancer. In patients with PJS, the risks of small-bowel cancer and obstruction are known, and screening may help avoid emergency surgery or cancer. Patients with PJS may require operative intervention for small-bowel obstruction or intussusception. Capsule endoscopy is superior to barium contrast study in detecting small-bowel polyps in patients with hereditary polyposis syndromes. Capsule endoscopy may help localize large polyps, which, in turn, may be removed by means of enteroscopy. Small-bowel neoplasia has been difficult to detect with standard methods but has been detected with capsule endoscopy. In a retrospective chart review of 562 patients undergoing capsule endoscopy for

various indications, Cobrin et al found that 8.9% were given a diagnosis of small-bowel tumor (eg, adenocarcinoma, carcinoid, GI stromal tumor, lymphomas, inflammatory polyp, lymphangioma, lymphangioectasia, hemangioma, hamartoma, and tubular adenoma) and 48% of the tumors were malignant.

**PROJECT TITLE:** A Phase 3, Open-Label Study to Evaluate the Safety and Efficacy of TMC435 plus Pegylated Interferon Alfa-2a and Ribavirin Administered for 12 weeks in Treatment-Naïve Subjects with Chronic Genotype 1 or Genotype 4 HCV Infection. RAC # 2141 018.

Source of Funding: Janssen Therapeutics EMEA

**PRINCIPAL INVESTIGATOR:** Hamad Al Ashgar, MD

### Overview of Study Design

This, multicenter, international study will evaluate the efficacy, tolerability, and safety of 12-week triple therapy with TMC435 plus PegIFN $\alpha$ -2a and RBV in treatment-naïve adult subjects with genotype 1 or genotype 4 chronic HCV infection and fibrosis stage equivalent to F0-F2. A target of 150 subjects with genotype 1 chronic HCV infection and 75 subjects with genotype chronic HCV infection will be assigned to treatment in this study.

In an attempt to enroll similar percentages of the 3 host IL28B genotypes (CC, CT or TT) as were enrolled in the ongoing Phase 3 TMC435 studies, the sponsor will make all effort to respect the following maximum caps for enrolment of each IL28B genotype for subjects with genotype 1 or genotype 4 HCV infection separately:

- a maximum of 35% of subjects with host IL28B genotype CC (i.e., maximum 35% IL28B CC among subjects with genotype 1 HCV infection and maximum 35% IL28B CC among subjects with genotype 4 HCV infection);
- a maximum of 55% of subjects with host IL28B

genotype CT (i.e., maximum 55% IL28B

- CT among subjects with genotype 1 HCV infection and maximum 55% IL28B CT among subjects with genotype 4 HCV infection);
- a maximum of 18% of subjects with host IL28B genotype TT (i.e., maximum 18% IL28B TT among subjects with genotype 1 HCV infection and maximum 18% IL28B TT among subjects with genotype 4 HCV infection).

In addition, within subjects infected with genotype 1 HCV, the sponsor seeks a balance between HCV genotypes 1a and 1b, therefore all effort will be made to cap enrolment of HCV genotype 1a at:

- a maximum of 50% of subjects infected with HCV genotype 1a.

Procedures to manage the distribution of the HCV genotype 1 subtypes and the host IL28B subtypes will be communicated to participating investigators at study initiation.

All subjects will start treatment at baseline (Day 1) and will receive triple therapy consisting of TMC435 plus PegIFN $\alpha$ -2a and RBV for 12 weeks. Total anti-HCV treatment duration will be response-guided based on HCV RNA levels at Week 2, Week 4, and Week 8 as follows:

- Subjects with host *IL28B* genotype CC will qualify for a total treatment duration of only 12 weeks (ie all anti-HCV treatment is discontinued after week 12) if the following criteria are met: if HCV RNA value is:
  - < 25 IU/mL (detectable or undetectable) at Week 2
  - < 25 IU/mL undetectable at Week 4
  - < 25 IU/mL undetectable at Week 8.
- Subjects with host *IL28B* genotype CT or TT will qualify for a total treatment duration of only 12 weeks (ie all anti-HCV treatment is discontinued after week 12) if the following criteria are met: if HCV RNA value is

- < 25 IU/mL undetectable at Week 2
- < 25 IU/mL undetectable at Week 4
- < 25 IU/mL undetectable at Week 8.
- if HCV RNA is above the threshold defined above at any of the 3 time points, subjects will continue PegIFN $\alpha$ -2a and RBV until Week 24.

Regardless of treatment duration, endpoint to evaluate efficacy will be SVR12.

The treatment continuation criteria will at all times be overruled if a subject meets any of the virologic stopping criteria outlined below. Subjects meeting any of the following criteria will be required to discontinue all treatment:

- Week 4: HCV RNA  $\geq$  25 IU/mL
- Week 12: HCV RNA  $\geq$  25 IU/mL OR < 25 IU/mL detectable
- a confirmed increase of > 1 log<sub>10</sub> IU/mL in HCV RNA level from the lowest level reached, or a confirmed HCV RNA level of > 100 IU/mL in subjects whose HCV RNA level had previously been < 25 IU/mL while on study drugs.

Detectable HCV RNA after previous undetectability should be confirmed by a confirmatory HCV RNA measurement within 2 weeks after receipt of the detectable HCV RNA value.

Treatment should only be discontinued after HCV RNA detectability is confirmed.

HCV RNA will be measured centrally and the results will be communicated to the investigational sites. It will be the investigator's responsibility to take the necessary actions regarding the discontinuation of therapy in case a virologic stopping rule has been met.

TMC435 will be taken as oral capsules of 150 mg. PegIFN $\alpha$ -2a and RBV will be given as

Pegasys and Copegus. Pegasys (180  $\mu$ g

once weekly) will be administered as weekly subcutaneous (SC) injections of 0.5 mL. The total daily dose of Copegus is weight-dependent. If body weight is < 75 kg, the total daily dose is 1000 mg, administered as 400 mg (2 tablets of 200 mg, morning intake) and 600 mg (3 tablets of 200 mg, evening intake). If body weight is  $\geq$  75 kg, the total daily dose is 1200 mg, administered as 2 x 600 mg (3 tablets of 200 mg per intake, morning and evening).

The study will be conducted in 3 phases: a screening phase of maximum 6 weeks, a treatment phase extending from Day 1 (baseline) up to 12 or 24 weeks depending on the response to treatment, and a posttreatment follow-up period of 24 weeks after the subject's last planned dose of study drug. The duration of the subject's participation (excluding screening phase) will vary between 36 weeks and 48 weeks, depending on the response to treatment.

Subjects should maintain the study visit schedule during treatment interruptions or after premature treatment discontinuation. Additional unscheduled visits may be performed for safety or tolerability reasons if needed. Interim analyses will be conducted. The key efficacy evaluation will be plasma HCV RNA levels. Safety evaluations will include the monitoring of AEs, physical examinations, vital sign measurements, clinical laboratory tests, and pregnancy testing. Patient-reported outcomes (PROs) will also be assessed.

A pharmacogenomic blood sample will be collected to allow for host IL28B genotyping. This

pharmacogenomic blood sample is mandatory and will be collected from all subjects who consent to participate in the study.

#### PRIMARY OBJECTIVES

**The primary objectives are:**

1. To determine the efficacy of TMC435 plus

PegIFN $\alpha$ -2a and RBV when administered for 12 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection, as Measured by the proportion of subjects with sustained virologic response 12 weeks after planned end of treatment (SVR12).

2. To assess the safety and tolerability of TMC435 plus PegIFN $\alpha$ -2a and RBV when administered for 12 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection.

#### MAJOR SECONDARY OBJECTIVES

##### Major secondary objectives are:

1. To determine the efficacy of TMC435 plus PegIFN $\alpha$ -2a and RBV when administered for 12 weeks in treatment-naïve subjects with chronic genotype 4 HCV infection, as measured by the proportion of subjects with sustained virologic response 12 weeks after planned end of treatment (SVR12).
2. To assess the safety and tolerability of TMC435 plus PegIFN $\alpha$ -2a and RBV when administered for 12 weeks in treatment-naïve subjects with chronic genotype 4 HCV infection  
Further major secondary objectives are in subjects with genotype 1 or genotype 4 HCV infection (separately per genotype):
3. To determine the proportion of subjects who achieve virologic response at Week 2 (W2VR) and the proportion of subjects who achieve RVR.
4. To determine the relationship between W2VR (HCV RNA <25IU/mL undetectable; HCV RNA <25IU/mL detectable; and combined) and SVR12 and between RVR and SVR12.
5. To determine the efficacy of TMC435 plus PegIFN $\alpha$ -2a and RBV for 12 weeks followed by 12 weeks of PegIFN $\alpha$ -2a and RBV (i.e., a total treatment duration of 24 weeks), as measured by the proportion of subjects with SVR12.
6. To determine the efficacy of TMC435 plus PegIFN $\alpha$ -2a and RBV after a total treatment duration of 12 weeks, as measured by the proportion of subjects with sustained virologic

response 24 weeks after planned end of treatment (SVR24).

7. To determine the efficacy of TMC435 plus PegIFN $\alpha$ -2a and RBV for 12 weeks followed by 12 weeks of PegIFN $\alpha$ -2a and RBV (i.e., a total treatment duration of 24 weeks), as measured by the proportion of subjects with SVR24.
8. To evaluate the evolution of HCV RNA levels at regular intervals during treatment and after planned end of treatment.

and for both genotypes combined:

9. To evaluate impact of HCV or its treatment on patient reported symptoms and functioning using a new patient reported outcomes tool, the Hepatitis C Symptom & Impact Questionnaire (HCV-SIQ) and four well-validated PRO instruments measuring severity and impact of fatigue (Fatigue Severity Scale, FSS), depressive symptoms (Center for Epidemiologic Studies Depression Scale, CES-D), time missed from work and impairment in daily activities (Work Productivity and Activity Impairment, WPAI: Hepatitis C), and health status (EuroQol 5 Dimension, EQ5D).

**PROJECT TITLE:** Effectiveness Of Radiofrequency Energy Delivery To The Gastro-Esophageal Junction In Refractory GERD Patients, A Prospective Controlled Therapeutic Trial. RAC 2141 096.

Source of Funding: KFSH & RC

**PRINCIPAL INVESTIGATOR:** Mohammed Qassem Khan

**PRINCIPAL CO-INVESTIGATOR:** Mohammed Al-Quaizl

**OTHER CO-INVESTIGATORS:** Adnan Al-Mahrouq, Saleh Al-Aqeel, Fahad Al-Sohaibani, Khalid Al-Kahtani, Abdulrahman Alfadda, Amir Butt, Hamad Al-Ashgar

**BACKGROUND:** Gastroesophageal reflux disease (GERD) is the most common principal gastroenterological diagnosis in the world, associated with a wide range of symptoms, typically heartburn, acid regurgitation, chest pain and dysphagia, while

severely impairing health related quality of life (HRQL). Acid suppression with proton pump inhibitors (PPIs) is the mainstay of therapy for GERD. It is known that resolution of esophageal mucosal inflammation is more likely to occur than resolution of symptoms. It has been estimated that between 10% and 40% of the patients with GERD fail to respond symptomatically, either partially or completely, to a standard dose PPI. Failure of the PPI treatment to resolve reflux symptoms has become one of the most common presentations of GERD in gastrointestinal clinical practice. As GERD is one of the most prevalent chronic disorders in the world, even a small proportion of GERD patients becoming therapy-resistant encompass a substantial part of the work load of general practitioners, internists and gastroenterologists. Long-term PPI use has been associated with a variety of adverse effects. These include bone fractures, community-acquired pneumonia, mineral and vitamin deficiency, major adverse cardiovascular events, and others.

A number of minimally invasive, lower cost, and lower risk endoscopic procedures have been introduced since 1998, aimed at improvement of the barrier function of the lower esophageal sphincter (LES), including Endocinch (Bard), Enteryx (Boston Scientific), Gatekeeper, Plicator NDO injection of sclerosants/collagen and radiofrequency (RF) modulation of the lower esophageal sphincter or Stretta procedure, as well as three additional surgical technologies including Esophyx (EndoGastric Solutions), Linx titanium magnets (Torax), and implantable LES stimulators (EndoStim).

Nearly all nonsurgical devices have been withdrawn from the market either due to ineffectiveness or complications, except for the Stretta device. The Stretta procedure delivers radiofrequency (RF) energy to the lower esophageal sphincter (LES), resulting in an increase in basal LES pressure and overall improvement in the anti-reflux barrier, improving GERD symptoms by reducing LES compliance, contributing to a possible beneficial decrease in refluxate volume. There is a significant decrease in

intra-esophageal pH as well as both proximal and distal esophageal acid exposure. Single, and more notably double-dose, Stretta therapy produces a more frequent normalization of GERD-HRQL, and a reduction in both the use of PPI medication and esophageal acid exposure.

In a meta-analysis, a comprehensive search was performed of all cohort series and randomized controlled trials (RCT) of Stretta procedure published in between 2000-2010. The meta-analysis reported on 18 studies included 1441 patients. The results show that RF treatment significantly improved heartburn scores (mean heartburn score decreased in each individual study and showed a significant change from 3.55 to 1.19 in the pooled analysis), and produced significant improvements in quality of life as measured by the GERD HRQL scale and the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire. Esophageal acid exposure decreased from a pre-procedure DeMeester score of 44.4 to 28.5 but did not normalize, and while the procedure did not significantly increase LES pressure, there was a trend toward improvement. The most common adverse outcomes encountered were minor and transient.

Recently, Noar et al. evaluated the long-term safety, efficacy, and durability of response to radiofrequency treatment of the lower esophageal sphincter (Stretta) in GERD patients with inadequate symptom control despite minimum twice-daily PPI therapy who underwent the Stretta procedure. They evaluated 217 patients before and after Stretta, GERD-HRQL scores, satisfaction, and PPI use significantly improved and results were immediate and durable at 10 years. No short term adverse events happened except 2 out of 217 patients developed minor, self-limited bleeding which required no intervention or transfusion, and throughout the 10-year study period no long-term adverse events developed.

It appears that radiofrequency delivery to the lower esophageal sphincter is a safe procedure

that effectively reduces symptoms in some patients. In contrast to the above reports, Dundon et al concluded that the radiofrequency energy delivery to the lower esophageal sphincter (Stretta procedure) does not provide long-term symptom control. However, The Stretta procedure was effective in reducing symptoms in 40% of patients, with a minimum of 36 month follow up or reduce medications use is seen in 20% to 50% of patients.

The U.S. FDA originally cleared the Stretta system for the use in 2000 and issued an updated clearance on the RF generator in 2011. Stretta therapy remodels the musculature of the LES and gastric cardia. Delivery of RF energy into tissue causes a circumscribed thermal coagulative necrosis that heals by fibrosis. Clinical studies demonstrate that the Stretta RF treatment results in significant reductions in tissue compliance and transient LES relaxations. These mechanisms act to restore the natural barrier function of the LES and to significantly reduce spontaneous regurgitation caused by transient inappropriate LES relaxations.

In Saudi Arabia, Stretta procedure is the newly introduced (2013) radiofrequency energy delivery technique for the treatment of long standing refractory GERD. In view of conflicting reports about the efficiency of the Stretta procedure particularly in refractory GERD patients, we decided to conduct a prospective control therapeutic trial for this revolutionary treatment. The patients with persistent GERD symptom on PPI had only two options; either go to surgical repair by Nissen fundoplication or undergo for this quite non-surgical safe endoscopic technique resulting in elimination or reduction in medication use, and may positively impact the disease progression.

**AIM AND OBJECTIVE:** The primary objective is to assess the effectiveness of the Stretta procedure in PPI refractory GERD patients, subjectively by improvement in GERD-HRQL related quality of life (using a validated questionnaire).

The secondary objective is the reduction or elimination of medication use, decrease in number of refluxes or bolus exposure time, and increase basal LES pressure after the radiofrequency application.

**PROJECT TITLE:** Elucidate the Mechanisms Through Which Febrile-Range-Hyperthermia Primes Neutrophils for Chemokine-Directed Trans-Vascular Egress. RAC # 214 1037.

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

**PRINCIPAL INVESTIGATOR:** Eid Mutairy, MD  
**CO-INVESTIGATORS:** Mohammad Khalid, MD

### Summary

Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is characterized by neutrophil (PMN)-rich inflammation, endothelial dysfunction, and epithelial injury. Only one therapeutic intervention, low tidal volume ventilation, has been shown to improve survival in ARDS, and mortality remains ~40%. Previous work showed that fever/hyperthermia may be another potential modifiable factor in the pathogenesis of ARDS. Preclinical studies demonstrate that exposure to febrile-range hyperthermia (FRH) enhances innate immune function by augmenting PMN recruitment and by facilitating transition from innate to adaptive immunity, especially in lung. However, the immunopotentiating effects of FRH also increase collateral tissue injury. Clinical associations between high fever and ALI in a wide range of clinical settings support the potential contribution of fever to ALI pathogenesis. Of particular relevance to healthcare in the Kingdom, ~25% of patients with heat stroke suffer ARDS, indicating that hyperthermia itself can trigger ALI. Prolonged is associated with ~ 3-fold higher mortality in critically ill patients. Collectively these data and others suggest that fever might increase ALI and suppressing fever might decrease ALI in humans. However, since FRH also accelerates pathogen clearance, fever suppression

may also impair innate immune defence, which is particularly concerning in critically ill patients who have indwelling foreign bodies and are exposed to multi-antibiotic resistant pathogens. These concerns support our search for an improved understanding of the immunomodulatory effects of FRH and development of more strategic approaches that selectively target the harmful effects of fever while preserving its benefit.

#### Aims of Study:

1. Determine how FRH exposure modifies capacity of PMNs for IL-8-induced tight binding to ICAM-1, chemotaxis and chemokinesis, TEM, and migration through subendothelial matrix.
2. Analyze the contribution of p38-dependent adhesion molecule expression to the FRH enhanced PMN migration capacity.
3. Analyze the effects of FRH and the contribution of p38 MAPKs on PMN cytotoxic potential in circulating PMNs.

We expect that the results of these studies will clarify the mechanisms by which FRH increases PMN capacity for extravasation, chemokine-directed recruitment, and cytotoxicity and the consequences for ALL.

#### LIST OF PEER-REVIEWED PUBLICATIONS FOR THE LAST 3 YEARS

- RAC # 2140 118: Althaf MM, Abdelsalam MS, Hussein M, Saddiq MS. *Brevibacterium casei* Isolated as a Cause of Relapsing Peritonitis. *BMJ Case Reports*. 2014 Mar 19;2014. pii: bcr2014203611.doi:10.1136/bcr-2014-203611.
- RAC # 2140 131: Mohammed Mahdi Althaf, Maged Hassan Hussein, Mohamed Said Abdelsalam, Sadiq Mohammed Amer. Case Report- Acute Kidney Injury in a Diabetic Hemophiliac on stap at a time. *BMJ Case Report* 2014. doi:10.1136/bcr-2014-203967.
- RAC # 2140 129: Mohamed Rashwan, Mohammed Mahdi Althaf, Mohamed Said Abdelsalam, Turki Al Hussain. Hoarsenes of Voice as the Herald of Granulomatosis with Polyangiitis. *BMJ Case Report* 2014. doi:10.1136/bcr-2014-203728.
- RAC # 2140 122: Mohammed Althaf, Mohammed Abdelsalam, Mohamed Rashwan, Quaid Nadri. Emphysematous pyelonephritis and cystitis in a renal transplant recipient. *BMJ Case Report*, 28 Sept 2014. doi:10.1136/bcr-2014-205589.
- RAC # 2111 095: Musthafa Chalikandy Peedikayil, Hamad Ibrahim Al Ashgar, Abdullah Al Mousa, Mohammed Al Sebayel, Khalid Al Kahtani, Faisal Aba Alkhail. "Liver transplantation in Wilson's disease: Single center experience from Saudi Arabia". *World J Hepatol* 2013 March 27; 5(3): 127-132.
- RAC # 2130 015: Alzahrani Ali (Corresponding Author), Al Qarawi Abdullah, Al Suhaibani Fahad, Al Mana Hadeel, Abalkhail Halah. Pancreatic metastasis arising from BRAF-positive papillary thyroid cancer: the role of endoscopic ultrasound-guided biopsy and response to sorafenib therapy. *Thyroid*. 2012 Mar 21. [Epub ahead of print]
- RAC # 2131058: Musthafa Peedikayil, Fahad Al Sohaibani, Abdullah Hamad Al Khenizan, "Levofloxacin-Based First-line Therapy versus Standard First-Line Therapy versus Standard First-Line Therapy for Helicobacter pylori Eradication: Meta-Analysis of Randomized Controlled Trials". *PLOS ONE* January 2014/ Volume 9/ Issue 1/ e85620.
- RAC # 2140 123: Mohammed Althaf, Mohamed Abdelsalam, Mohamed Rashwan, Quaid Nadri. Acute Hepatitis C Infection in a Renal Transplant Recipient: Primacy of the Liver of Kidney? *BMJ Case Report* 2014. Doi:10.1136/bcr-2014-203643.
- RAC # 2140 113: Althaf MM, Abdelsalam MS, Quaid JN.. Severe Vascular Calcification and Gangrene in a Hemodialysis Patient. *BMJ Case Reports*. 2014 Feb 21; doi: 10.1136/bcr-2013-203258

# THE ONCOLOGY CENTRE



## ONCOLOGY CENTRE

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**K**FSH&RC enjoys the recognition of having the largest cancer facility in the Gulf region where more than 2,691 new patients were treated in 2013. Established with a mission of providing excellent cancer treatment, education and research, the Oncology Centre evolved over the years towards its vision of becoming one of the best international centers for cancer research, prevention, and treatment. Accredited by the World Health Organization (WHO) as a Collaborating Centre for Cancer Prevention and Control, cancer patients are assessed in multidisciplinary clinics and provided with treatment in accordance with disease specific internationally accepted management guidelines. Our oncologists continue to actively address national oncology problems through their involvement in institutional, national, and international research protocols with the invaluable support of the Oncology Research Unit (ORU) which also serves as a hospital base for cancer and bone marrow transplantation registries.

**Mohammed Mohiuddin, MD**  
DIRECTOR

**Mahmoud Aljurf, MD**  
DEPUTY DIRECTOR

**Fahad AlMohareb, MD**  
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**Shouki Bazarbashi, MD**  
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**Mohammed Al-Shahri, MD**  
Head of Palliative Medicine

**Tarek Amin, MD**  
Head of Surgical Oncology

**Naeem Chaudhri, MD/  
Fazal Hussain, MD**  
Co-Head of Research Unit

**MAJOR ACHIEVEMENTS FOR THE YEAR INCLUDE:**

- Continued institutional membership and collaborative studies with Southwest Oncology Group (SWOG), American College of Radiology Imaging Network (ACRIN), and Radiation Therapy Oncology Group (RTOG)/NRG Oncology. Highest accruing institution on RTOG protocol 0417.
- Continued membership of the CBMTG (Canadian Bone Marrow Transplantation Group) and the EBMT Clinical Trials Group (EBMT); highest accruing institution on CBMTG protocol 0601.
- Eastern Mediterranean Blood & Marrow Transplantation Group (EMBMT) flourished. Myriad of disease site Working Committees expanded to encompass new trials. Several research protocols in progress. Several manuscripts published in major international Bone Marrow Transplantation Journals. Significantly increased research studies and publications; 49 on-going research projects and 5 new study proposals.
- Gulf Oncology Regional Group (GORG) formed in KFSH&RC: Successfully completed GORG-001 and GORG-002.
- Continue to receive investigational drugs from National Cancer Institute (NCI) for patients on clinical trials.
- Intensity Modulated Radiation Therapy (IMRT), Image-guided Radiation Therapy (IGRT) credentialing by Radiological Physics Center (RPC) at MD Anderson Cancer Center, USA.
- Intra-Operative Radiation Therapy (IORT) Program; fully operational.
- Fully functional Tomotherapy, Cyberknife and 3 linear accelerators with a wide range of photo and electron energies and imaging techniques to treat intricate cancer patients.
- Operational Brachytherapy suite for HDR.
- Introduced Deep Inspiration Breath Hold (DIBH); a cardiac sparing technique to treat left-sided breast cancer.
- Initiated Gold plaque Iodine125 brachytherapy treatment for eye tumor in collaboration with King Khaled Eye Specialist Hospital and King Abdulaziz University Hospital.
- Continue to serve as Center of Excellence (COE) for Breast cancer and Lymphoma.
- Regularly held Oncology Center's Clinical Research Committee (CRC) meetings to help expedite clinical research; a mirror committee of hospital CRC.
- Organized 1<sup>st</sup> Hematology Board Review Course on Thrombosis and Hemostasis on 5-6 September 2014.
- Conducted Adult Hematology Symposia Series: 1<sup>st</sup> Adult Hematology Mini-Symposium on Infectious Complications in Hematological Malignancies on 25 June 2014.
- Held Medical Physics IAEA Conference and training work shop; Established IAEA Collaborative Centre in Radiation Medicine for Radiation Physics residency program.
- Accomplished 8<sup>th</sup> Oncology Academic and Research Day on 8 May 2014; attended by large number of researchers.
- Society of Clinical Research Associates (SOCRA) Saudi Arabia chapter was established to meet the educational and training needs of clinical research staff in the entire MENA region: First Certification exam was conducted in KFSH&RC in Sept 2014.
- Advanced Research Review Course for Certified Clinical Research Professional (CCRP) certification was held on 5 June 2014.
- Eastern Mediterranean Blood and Marrow Transplantation (EMBMT) meeting was held in collaboration with EMBMT in Milan, Italy from 30 March-2 April 2014.

**FUTURE RESEARCH DIRECTION**

- Promote well designed clinical/transitional research activities.
- Establish firm collaboration with Research Center and other loco-regional and international partners to promote translational research.
- Continue robust research collaboration with international groups.
- Expand and maximize utilization of available database for certain tumor sites in research direction and bench marking.

- Continue educational activities for Clinical Research Coordinators for standardization.
- Spearhead international collaboration for Tumor Sampling/Repository with NCTN to answer important scientific questions.
- To host international symposia with emphasis on clinical research.
- To conduct more pioneering scientific research to advance cancer treatment and care.
- To work with the latest and emerging technologies to provide the most advanced and optimum cancer treatments.
- Ensure continuous availability of emerging and evolving therapies and drugs through clinical trials at KFSH&RC.
- Initiate Quality of life (QOL) trials.
- Continue to serve as a University Hospital Clinical research platform for Alfaisal University.
- Commence Oncology Research Fellowship Program
- Embark on Cardio-Oncology Program.
- Center of Excellence (COE) for Leukemia, Colorectal, Thrombosis and Hemostasis Service.

### LIST OF ONGOING RESEARCH ACTIVITY

TITLE	PI	RAC #
Establishment of Acute Lymphocytic Leukemia Data Base in the Department of Oncology	Chaudhri	2021-051
Establishing a Data Base for Aplastic Anemia and Other Marrow Failure Syndrome	H. Al-Zahrani	2021-084
Induction of Mixed Hematopoietic Chimerism in Patients Using Fludarabine, Low Dose TBI, PBSC Infusion and Post Transplant Immunosuppression with Cyclosporin and Mycophenolate	Aljurf	2001-051
Ewings RAC#931-025 Dr. Memon (EORTC)	Memon	931-025
CBMTG 0601: A Randomized Multicentre Study Comparing GCSF Mobilized Peripheral Blood and GCSF stimulated Bone Marrow in patients Undergoing Matched Sibling Transplantation for Hematologic Malignancies.	Aljurf	2081-076
ENESTxtnd: Extending Molecular response with Nilotinib in newly diagnosed chronic myeloid leukemia (CML) patients in chronic phase.	N. Chaudhri	2101-102
EBMT/CLWP non-interventional prospective study on effects of 2 <sup>nd</sup> generation TKI on outcome of allotx in CML.	Al-Jurf	2051-056
Biomarkers IN Chronic Graft vs. Host Disease (cGVHD).	Al-Jurf	2101-101
MPN Registry	H. Al-Zahrani	2131-016
Prospective Burkitt's Lymphoma database	W. Rasheed	2131-026
Nasopharyngeal Carcinoma Database.	Al Rajhi	2051-017
International Bone Marrow Transplant Registry (Allogeneic Transplant).	Al-Jurf	2141-054
European Bone Marrow Transplant Registry.	Al-Jurf	2141-054
International Bone Marrow Transplant Registry (Autologous Transplant).	Al-Jurf	2141-054
RTOG 1174: A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: THE OUTBACK TRIAL	Al Hussaini	2131-039
RTOG 0631: Phase II/ III Study of Image-Guided Radiosurgery/SBRT for Localized Spine Metastasis	Al Rajhi	2091-073
RTOG 0417: A Phase II Study of Bevacizumab in Combination with Definitive Radiotherapy and Cisplatin Chemotherapy in Untreated Patients with Locally Advanced Cervical Carcinoma.	Al Rajhi	2081-012

TITLE	PI	RAC #
RTOG 0920: Phase III Study Of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer.	Al Rajhi	2101-074
RTOG 01008: A Randomized Phase II Study of Adjuvant Concurrent Radiation and Chemotherapy versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors	Al Rajhi	2111-096
RTOG 1119: Phase II Randomized Study of Whole Brain Radiotherapy in Combination with Concurrent Lapatinib in Patients with Brain Metastasis from Her2-Positive Breast Cancer A Collaborative Study of RTOG and KROG	Shabanah/ Kausar	2131-030
RTOG 1203: A Randomized Phase III Study of Standard VS IMRT Pelvic radiation for Post-Operative Treatment of Endometrial and Cervical Cancer (TIME-C)	R Mahmoud	2131-029
A Phase II Trial of Docetaxal and Cisplatin versus Low-Dose Fractionated Radiation plus Docetaxal and Cisplatin as induction Therapy in locally advanced Nasopharyngeal Cancer	Al Rajhi	2121-063
(GIST): A multi-center, single arm, phase II study of adjuvant imatinib (Glivec™) in patients following the resection of primary gastrointestinal stromal tumor.	Memon	2091-053
(EVERMORE): An open-label, multi-center phase 2 study to evaluate everolimus as monotherapy treatment for patients with metastatic recurrent and/or unresectable renal cell carcinoma.	Bazarbashi	2101 002
A Phase III Trial of Capecitabine (Xeloda), Oxaliplatin and Irinotecan in Combination with Bevacizumab in 1 <sup>st</sup> Line Treatment of Metastatic Colorectal Cancer	Bazarbashi	2081-068
PET EVALUATED NEO-ADJUVANT THERAPY (PENAT) TRIAL: A randomized trial comparing pre-operative chemo-radiotherapy with Cisplatin and Fluorouracil versus Chemotherapy with Doxetaxel and Irinotecan in PET non responders resectable cancer esophagus: a multicenter study.	Bazarbashi	2111-104
Molecular Classification of Breast Carcinoma by Immunohistochemical Analysis. Are we different? (A retrospective study).	Twegieri/ Tulbah	2101- 027
Treatment of Neuroendocrine tumors (NETs) with Combination of Everolimus and Radiolabeled Somatostatin Analogue.	AlJubran	2121-159
A Phase 2 Trial Evaluating The addition of High dose ( SFGRT ) Spatial Fractionated Grid Radioinduction Therapy in patients with Advanced and Bulky Soft Tissue Sarcomas ( >5 cm ) Treated with Pre Operative Radio-Chemotherapy.	Mohiuddin	2121-088
(PERUSE): A Multicenter, Open-Label, Single-Arm Study of Pertuzumab in Combination with Trastuzumab and a Taxane in First Line Treatment of Patients with HER2-Positive Advanced (Metastatic or Locally Recurrent) Breast Cancer.	Twegeiri	2121-060
S0702: 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.	Rasheed/ Kausar	2111-094
Locally Advanced High Grade Extremity Soft Tissue Sarcoma- Enhanced Response Novel Approach to Neo Adjuvant Chemo-Radiation using Induction Spatially Fractionated GRID Radiotherapy (SGFRT)	Mohiuddin	2141 019
Phase II Study of Neo-adjuvant Chemoradiotherapy using infusional Gemcitabine followed by Surgery for Locally Advanced(T3 and T4) Rectal Adenocarcinoma.	Bazarbashi/ Mohiudin	2141 124
Phase III Combined Alternating Sunitinib and Bevacizumab (AVASTIN) in Advanced Renal Cell Carcinoma (CASA)	Bazarbashi	2141 102
Data collection for Breast cancer (1992 - 2012 ).	Ajarim	2051-029
Data collection for newly Dignosed Hodgkin and Non Hodgkin Lymphoma	S. Akhtar	2021-048

TITLE	PI	RAC #
The Prognostic Significance of BCL2 & BCL6 Expression in DLBCL treated by CHOP or R-CHOP. Retrospective Study, Single Institute Experience	Soudy	2071-061
Auto BMT ,lymphoma cases	S. Akhtar	2121-011
Retrospective analysis to check frequency of pregnancies in females post BMT	S. Akhtar	2111-093
Prospective data collection of newly diagnosed sarcoma cases	Memon	2081-015
SWOG Q230: Phase III Trial of LHRH Analog Administration During Chemotherapy to Reduce Ovarian Failure Following Chemotherapy in Early Stage, Hormone-Receptor Negative Breast Cancer.	Al Sayed	2091-013
PNH Registry	Al Mohareb	2131-049
E2108: A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer.	Suleman/ Shabanah	2121-015
Prospective Database for Acute Myeloblastic Leukemia	Osman / Chaudhri	2051-057
T3151 and any other mutation in the BCR-ABL Kinase Domain: Frequency And Clinical Outcome In Patients With Chronic Myeloid Leukemia	Chaudhri	2131-150
The Proteome Profile of Aplastic anemia	Aljurf	2060-021
The Proteome Profile of Acute Myeloid Leukemia (AML) Patients in Saudi Arabia	Dr.Amer / Dr.Ayodele	2130-010
Prospective Database for Chronic Myelogenous Leukemia.	Chaudhri	2051-056
E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).	Chaudhri	
S1007: A Phase III, Randomized Clinical Trial Of Standard Adjuvant Endocrine Therapy +/- Chemotherapy In Patients With 1-3 Positive Nodes, Hormone Receptor-positive And Her2-negative Breast Cancer With Recurrence Score Of 25 Or Less. RxPONDER:A Clinical Trial RX for Positive Node, Endocrine Responsive Breast Cancer.	Suleman	
E1412: Randomized Phase II Open Label Study of Lenalidomide R-CHOP (R2CHOP) vs RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma.	Rauf	
NRG-HN002: A Randomized Phase II Trial for Patients with p16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer, NCT02254278.	Al Rajhi	

## PUBLICATIONS

### SECTION OF ADULT HEMATOLOGY & HEMATOPOIETIC STEM CELL TRANSPLANTATION

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- Allogeneic Hematopoietic Stem Cell Transplantation in Fanconi Anemia: The EBMT Experience. *Blood.* 2013 dec 19;122(26):4279-86. doi: 10.1182/blood-2013-01-479733. Epub 2013 Oct 21.

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- The impact of HLA unidirectional mismatches on the outcome of myeloablative hematopoietic stem cell transplantation with unrelated donors. *Blood* 2013 Jun 6;121(23):4800-6. doi: 10.1182/blood-2013-01-480343. Epub 2013 May 1.
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- Global Hematopoietic Stem Cell Transplantation (HSCT) At One Million: An Achievement of Pioneers and Foreseeable Challengers for the Next Decade. A Report from the Worldwid Network for Blood and Marrow Transplantation (WBMT) Abstract # 3355, 55<sup>th</sup> ASH Annual Meeting and Exposition, 7-10 December 2013
- Dietger Niederwieser, MD, Marcelo C Pasquini, MD, MS, Mahmoud D. Aljurf, MD, Dennis L. Confer, MD, Helen Baldomero, Luis Fernando Bouzas Sr., MD, MSC, PhD, Mary M. Horowitz, MD, MS, Minako Iida, Yoshihisa Kodera, Jeffrey H. Lipton, MD, PhD, Machteld Oudshoorn, Eliane Gluckman, MD, Jakob R. Passweg, Jeffrey Szer, MD, Nicolas Novitzky, MD, PhD, Jon J. van Rood, MD, Luc Noel, J. Alejandro Madrigal, MD, PhD, Karl Frauendorfer, Alois Gratwohl and Frederick R. Appelbaum, MD .
- Prediction of Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) Related Mortality in Acute Leukemia: Generation of a Machine Learning-Based Model Using The Data Set of the Acute Leukemia Working Party (ALWP) of the EMBT. Abstract # 409, 55<sup>th</sup> ASH Annual Meeting and Exposition, 7-10 December 2013
- Roni Shouval, MD, Myriam Labopin, MD, Ori Bondi, Hila Mishan Shamay, MSc, Avichai Shimoni, MD, Fabio Ciceri, MD, Jordi Esteve, MD, PhD, Sebastian Giebel, MD, Norbert-Claude Gorin, MD, PhD, Christoph Schmid, MD, Imane Zakaria, Leila Moukhtari, Emmanuelle Polge, Mahmoud Al-Jurf, MD, Nicolaus Kröger, MD, Charles Craddock, MD, Andrea Bacigalupo, MD, Jan Cornelissen, MD, PhD, Frederic Baron, MD, PhD, Ron Unger, PhD, Arnon Nagler, MD, MSc and Mohamad Mothy,

## SECTION OF ADULT HEMATOLOGY & HEMATOPOIETIC STEM CELL TRANSPLANTATION

### ABSTRACTS 2013

- A Canadian Blood and Marrow Transplant Group (CBMTG) Randomized Trial Comparing G-CSF Mobilized Peripheral Blood Versus G-CSF Stimulated Bone Marrow in Recipients of Sibling Allografts For Hematologic Malignancies. Abstract 709, 55<sup>th</sup> ASH Annual Meeting and Exposition, 7-10 December 2013
- Stephen Couban, MD, Mahmoud Aljurf, Silvy Lachance, MD, Irwin Walker, MBBS, Cynthia L. Toze, MD, FRCP(C), Morel Rubinger, MD, Jeff H. Lipton, PhD, MD, Stephanie J. Lee, MD, MPH, Jeffrey Szer, MD, Richard Doocey, Ian D Lewis,

- MD, PhD
- Autologous Stem Cell Transplantation for Adult Burkitt Lymphoma in the Rituximab Era: A Retrospective Study of the Lymphoma Working Party (LWP) of the European Group for Blood and Marrow Transplantation (EBMT). Abstract # 3368, 55<sup>th</sup> ASH Annual Meeting and Exposition, 7-10 December 2013
  - Syed Ahmed, MRCP, FRCPath, Ariane Boumendil, PhD, Herve Finel, Anna Sureda, MD, PhD, Harry C. Schouten, MD, PhD, Mohamad Mohty, MD PhD, Guustaaf van Imhoff, Wilfried Schroyens, MD, PhD, Jurgen Finke, Nicolaas PM Schaap, MD, PhD, Ignazio Majolino, Prof, Mario Bargetzi, MD, Enrico Maria Pogliani, MD, Boris Afanasyev, Peter Dreger, MD and Mahmoud D. Aljurf, MD
  - Outcome of Aplastic Anemia in Adolescence. A Survey of the Severe Aplastic Anemia Working Party (SAAWP) of the European Blood and Bone Marrow Transplant Group (EBMT) Abstract # 2481, 55<sup>th</sup> ASH Annual Meeting and Exposition, 7-10 December 2013
  - Carlo Dufour, MD, Marta Pillon, MD, Jakob Passweg, MD, Gérard Socié, MD, PhD, Andrea Bacigalupo, MD, Genny Franceschetto, Rosi Oneto, Antonio M. Risitano, MD, PhD, Régis Peffault de la Tour, MD, PhD, Andre Tichelli, MD, Alicia Rovo, MD, Christina Peters, Britta Hochsmann, MD, Hubert Schrezenmeier, MD, PhD, Mahmoud D. Aljurf, MD and Judith Marsh, MD
  - Expression Proteomics as Surrogate Biomarkers for Early Treatment Response in Chronic Myeloid Leukemia (CML) Patients. Abstract # 4016, 55<sup>th</sup> ASH Annual Meeting and Exposition, 7-10 December 2013
  - Ayodele Alaiya, MD, MPH, PhD, Naeem Chaudhri, MD, Tarek Owaidah, MD, FRCPA, Jonathan Fox, PhD, Zakia Shinwari, MSc, Eman Barhoush, BSc, Fahad Alsharif, MD, Said Y Mohamed, MD, Walid Rasheed, MD, Feras Alfraih, MD and Mahmoud Aljurf, MD
  - Survival Improvements Following Myeloablative Allogeneic Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia in Adolescents and Young Adults Have Been Comparable to Younger Children: A Study from the CIBMTR Abstract # 554, 55<sup>th</sup> ASH Annual Meeting and Exposition, 7-10 December 2013
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  - Current Outcome of HLA Identical Sibling Vs Unrelated DONOR Transplants in Severe Aplastic Anemia: AN EMBT Analysis. Abstract # 707, 55<sup>th</sup> ASH Annual Meeting and Exposition, 7-10 December 2013
  - Andrea Bacigalupo, MD, Gérard Socié, MD, PhD, Rose-Marie Hamjladi, Mahmoud Aljurf, A Mashan, Slawomira Kyrz-Krzemien, MD, A Cybicka, H Sengeloev, Ali Unal, MD, Dietrich Beelen, MD, A Locasciulli, Carlo Dufour, MD, Jakob R. Passweg, R Oneto and Judith Marsh
  - Hematopoietic Cell Transplantation (HCT) for Severe Aplastic Anemia (SAA): Impact of Graft Source and Economic Regions. Abstract # S599, 18<sup>th</sup> Congress of European Hematology Association, 13-16 June 2013
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## SECTION OF MEDICAL ONCOLOGY

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- Ali Jubran, et al. New challenges in communication with cancer patients in Springer,

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## SECTION OF RADIATION ONCOLOGY

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#### ABSTRACTS 2013

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- Locally advanced high grade extremity soft tissue sarcoma—enhanced response with novel approach to neoadjuvant chemo-radiation using induction spatially fractionated GRID radiotherapy (SFGRT)
  - Mohammed Mohiuddin, Muhammad Memon, Ahmed Nobah, Medhat Elsebaie, Abdullah Alsuhaibani, Rajive Pant, Mahmoud Shaheen,

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#### SECTION OF PALLIATIVE CARE MEDICINE

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- The Use of Anti-Diabetic, Anti-Hypertensive and Lipid-Lowering Medications in the Elderly Dying with Advanced Cancer. The 21<sup>st</sup> International Conference of Indian Association of Palliative Care, Acharya Harihar Regional Cancer Centre, Bhubaneswar, Orissa, India
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# THE OPHTHALMOLOGY DEPARTMENT



## OPHTHALMOLOGY DEPARTMENT

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The Ophthalmology Department at King Faisal Specialist Hospital & Research Center (KFSH&RC) continuously strives 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.

Our department has a history of international clinical research in eye diseases and is involved in several ongoing departmental and inter-departmental projects. We have participated in a variety of prospective and retrospective studies and reported cases and case series of local, national and international interest. Collectively, these studies will contribute to understanding the natural course of eye diseases, the long-term outcomes of treatment, and the epidemiology and genetics of eye diseases and vision loss in Saudi Arabia.

**Mohammed Mohiuddin, MD**  
DIRECTOR

**Mahmoud Aljurf, MD**  
DEPUTY DIRECTOR

**Fahad AlMohareb, MD**  
Head of Hematology/HSCT

**Shouki Bazarbashi, MD**  
Head of Medical Oncology

**Mohammad Al-Shabanah, MD**  
Head of Radiation Oncology

**Mohammed Al-Shahri, MD**  
Head of Palliative Medicine

**Tarek Amin, MD**  
Head of Surgical Oncology

**Naeem Chaudhri, MD/  
Fazal Hussain, MD**  
Co-Head of Research Unit

At the end of 2014, our department has three (3) international publications, four (4) poster presentations and eight (8) RAC-approved ongoing projects. It is our goal to expand descriptive and investigative research by having at least three (3) to four (4) active research projects every year, in collaboration with the Research Centre and other departments at KFSH&RC and to be recognized as a center of excellence in the Research international arena.

## RESEARCH PROJECTS

**PROJECT TITLE:** Genetics of Vision Impairment in Saudi Arabia. RAC Proposal #: 2070023.

**PRINCIPAL INVESTIGATOR:** Dr. Fawzan Al Kuraya

**CO-PRINCIPAL INVESTIGATOR:** Dr. Selwa Al Hazzaa

**PROJECT DESCRIPTION:** Vision loss (blindness and vision impairment included) is an important disabling condition among Saudis with significant medical, economic and social impact. Genetically determined conditions contribute significantly to the pool of vision loss in the Kingdom particularly among children where their frequency approaches 70%. This usually high frequency is the result of several factors the most common important of which is the high frequency of autosomal recessive disorder (many of which will inevitably involve the complex organ of the eye) as a result of high degree of inbreeding and consanguinity. Our research group has an extensive experience in mapping mendelian disorders, including genetic eye conditions. Similarly, we have solid experience in clinical, molecular and developmental genetics. We propose to focus our existing expertise in Saudi Arabia. Characterization these mutations will have an obvious impact on the medical care of the affected individuals since it makes prenatal/preimplantation diagnosis available options but it also represents a step in the right direction to this approach. In addition, 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 exciting opportunity to better understand the molecular mechanisms that govern human eye formation 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 that will recruit and study any eye condition that is likely to have a genetic underlying defect. Eye disorders the underlying genetic lesion of which is known will also be included since the spectrum of mutations among Saudi could, and in fact has been shown in many instances to, be different.

**PROGRESS:** On-going.

**PROJECT TITLE:** Characterization of the Molecular Basis of Hereditary Deafness in the Saudi Population. RAC Proposal #: 2080024.

**PRINCIPAL INVESTIGATOR:** Imtiaz F

**CO-PRINCIPAL INVESTIGATOR:** Al-Hazzaa SAF, Taibah K, Ramzan K, Al-Owain M, Bin Khamis G

**PROJECT DESCRIPTION:** Recessively inherited diseases are more prevalent in population where consanguineous marriages are common, like Saudi Arabia. Deafness is the most common sensory deficit in humans (1: 1000 child births) with both genetic (50%) etiologies. Our study hopes to define the genetics of non-syndromic and syndromic deafness in this population. Families with profound congenital deafness and an autosomal recessive mode of inheritance are a powerful resource for genetic linkage studies of recessively inherited deafness. The most common forms of hereditary deafness, their incidence and distribution in the Saudi population will be identified as the result from the study. The benefit of this study is also to provide knowledge and awareness through screening of carrier status and genetic counseling, therapy will have a major impact upon early intervention for and prevention of hereditary deafness.

**PROGRESS:** On-going.

**PROJECT TITLE:** A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multinational Clinical Study to evaluate the Efficacy and Safety of 2.0 mg/kg/week and 2.0mg/kg/every other week BMN 110 in patients with Mucopolysaccharidosis IVA (Morquio A Syndrome). (Protocol Number: MOR-004, IND: BMN 110, EudraCT number: 2010-0210198-18). RAC Proposal #: Protocol Number: MOR-004, IND: BMN 110, EudraCT number: 2010-0210198-18).

**PRINCIPAL INVESTIGATOR:** M. Al Sayed

**CO-PRINCIPAL INVESTIGATOR:** N. Awada, R Moslmani, L Al-Otaibi, S. Al Hazzaa

**PROJECT DESCRIPTION:** Mucopolysaccharidosis IVA (Morquio A syndrome, MPS IVA) is an inherited autosomal recessive disorder characterized by deficient activity of N-acetylgalactosamine-6-sulfatase (GALNS), resulting in macroscopic accumulation of the glycosaminoglycan (GAG) keratan sulfate (KS) in tissue macrophages, hyaline cartilage and other connective tissues, heart valve, and cornea as well as excretion in the urine. This accumulation causes multiple clinical manifestations including impaired functional capacity, endurance, and quality of life. There is currently no standard accepted treatment for MPS IVA other than supportive care. Enzyme replacement therapy with BMN 110 (rhGALNS) may be a potential new treatment option for MPS IVA patients. BMN 110 is expected to reduce the progressive accumulation of KS and improve signs and symptoms of the disease.

**PROGRESS:** Completed (Vimizim drug has been approved by FDA and officially is been prescribed to patients).

**PROJECT TITLE:** Optic Atrophy in Saudi Arabia. RAC Proposal #: 2141001.

**PRINCIPAL INVESTIGATOR:** Joyce N Mbekeani, FRCS, FRCOphth

**CO-PRINCIPAL INVESTIGATOR:** Maaly Abdel Fattah, Selwa A Al Hazzaa

**PROJECT DESCRIPTION:** Determine the causes of optic atrophy in the Saudi population as represented by the countrywide referrals to KFSH&RC. Optic atrophy is a common ophthalmic manifestation in our clinics and on the consult service and is associated with blindness (<20/400) of visual impairment (<20/60). It is not a diagnosis but represents permanent retinal ganglion cell loss, a significant and terminal sign that warrants further investigation to establish pathogenesis and etiology. A recent study<sup>1</sup> has detailed a hereditary form of optic atrophy in Saudi Arabia, whilst others have looked at blindness as a whole, including optic atrophy<sup>2-5</sup>. Although hereditary and syndromic forms are important and may account for a significant portion of pediatric causes, a full epidemiologic study is essential to determine the full range of causes of optic atrophy in the Saudi population. We have noticed a multitude of causes, so far, including primary hereditary forms, inborn errors of metabolism, trauma, large brain tumors impinging on the visual pathway and iatrogenic effects. KFSH&RC is well- placed to conduct broad studies since it has a large catchment area, receiving countrywide referrals and being in the position to conduct advanced investigations and make difficult diagnosis. Knowledge gained from this study will assist in forming the bases for future assignment of resources, inclusion in interventional (e.g stem cells, idebenone ) trials, assist in designing public health awareness campaigns for prevention and early diagnosis and design and provision of Low Vision Aids.

**PROGRESS:** On-going.

**PROJECT TITLE:** Ophthalmic Consultations in a Large Specialist Hospital. RAC Proposal #: 2141040.

**PRINCIPAL INVESTIGATOR:** Jeylan El Mansouri, MD

**CO-PRINCIPAL INVESTIGATOR:** Maaly Abdel Fattah, Selwa A Al Hazzaa

**PROJECT DESCRIPTION:** To profile all in-patient and ER consultations evaluated and managed by

the ophthalmology department at KFSH&RC. All consecutive in-patient and ER consultations evaluated and managed by the ophthalmology department (consultants and assistant consultants) will be documented and the information collected, commenced on March, 2014. Specific data: age, service requesting consult, reason for consult, type of consultation, final diagnosis and action required will then be tabulated.

**PROGRESS:** On-going (collected data including 350 patients).

**PROJECT TITLE:** Visual Impairment and Blindness in Saudi Arabia. RAC Proposal #: 2141044.

**PRINCIPAL INVESTIGATOR:** Amani Al Jassas, Optometrist  
**CO-PRINCIPAL INVESTIGATOR:** Maaly Abdel Fattah, Selwa A. Al Hazzaa

**PROJECT DESCRIPTION:** To determine the causes 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 causes 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 manpower, 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 resources, streamlining management for better quality of care and assist in designing public health awareness campaigns for the prevention and early diagnosis of vision loss. Furthermore, design and provision of Low Vision Aids and social support can be targeted to appropriately identify the sub-groups of our population.

**PROGRESS:** On-going.

**PROJECT TITLE:** Efficacy of AMBLYZ for Treatment of Mild Amblyopia. RAC Proposal #: 2141045.

**PRINCIPAL INVESTIGATOR:** Amani Al Jassas, Optometrist  
**CO-PRINCIPAL INVESTIGATOR:** Hachemi Nezar, Selwa A Al Hazzaa

**PROJECT DESCRIPTION:** To determine the efficacy of the new Amblyz liquid crystal glasses for the treatment of strabismic amblyopia 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 children regain vision. Several methods are currently in common use, the most frequent of which is adhesive patching. Where this is not possible, blurring of the healthy eye or penalization is achieved by optical or cycloplegia. The major drawback to these therapeutic interventions is the stigma suffered by the child, who may be non-compliant whilst at school or otherwise unsupervised. Other unintended consequences include skin irritation from the 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:** On-going.

**PROJECT TITLE:** Education in Glaucoma in a Tertiary Hospital in Saudi Arabia. RAC Proposal #: 2141065.

**PRINCIPAL INVESTIGATOR:** Jeylan El Mansouri, MD, FRCS  
**CO-PRINCIPAL INVESTIGATOR:** Maaly Abdel Fattah, Selwa A. Al Hazzaa

**PROJECT DESCRIPTION:** 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 patients' 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 these factors contribute to discourage patients from using the medications 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:** On-going

**PROJECT TITLE:** Evaluation of Macular Changes After Uneventful Phacoemulsification Surgery in Diabetic Patients Using Optic Coherence Tomography. RAC# 2141006.

**INVESTIGATOR:** Dr. Maaly Abdulfataah

**PROJECT DESCRIPTION:** Data collection is ongoing.

## PUBLICATIONS

- Neonatal Molybdenum Cofactor Deficiency and Ectopia Lentis in a Saudi Arabian Patient: Al Obaidallah M, Dogar M, Mbekeani J, Al Hazzaa S, September 2014.
- Efficacy of BOTOX as primary management of various strabismus. Abdulfataah M. Submitted to *IJPAM*.
- Relapsing chronic myelogenous leukemia presenting with bilateral optic nerve sheath infiltration. Abdulfataah M. Submitted to

*Hematology/Oncology & Stem Cell Therapy* – Hospital journal August 2014 (Publication# 2140184).

- Variable expression pattern in Donnai - Barrow syndrome: report of two novel LRP2 mutations and review of the literature. Abdulfataah M, Khalifa O, Accepted in *European Medical Genetic Journal*.

## SUBMITTED PUBLICATIONS

- Papillary Tumor of the Pineal Region Presenting with Foster Kennedy Sign: Joyce Mbekeani, Manzoor Ahmed, Maher, Hassounah, Khaled Abdul Shafi, Selwa Al Hazzaa, re-submitted to *Hematology / Oncology & Stem Cell Therapy*, Pub No. 2130286.
- Bilateral Optic Nerve Sheath Metastases from Signet Cell Adenocarcinoma: Joyce N Mbekeani, Mohammed Qureshi Haseeb, Mohammad Asif Dogar, Asma Mahmoud Tulbah, Salem Hani Hamed, Selwa A Al Hazzaa, re-submitted to *Journal of Neuro-ophthalmology*, Pub No 2130287.

## POSTER PRESENTATIONS

- Ophthalmic Imaging Challenges in Saudi Arabia, International Conference on Ophthalmic Photography, Toronto, Canada, May 2014.
- Ophthalmic Care; Saudi Arabian Experience, International Conference on Ophthalmic Photography, Toronto, Canada, May 2014.
- Pilocyctic Astrocytoma: Ophthalmic and Neuro-Radiologic Manifestations, American Academy of Ophthalmology, October 2014.
- Combined Nasolabial and Glabellar Flaps for Reconstruction of large Medial Canthal Defects: Ten Years' Experience, American Academy of Ophthalmology, October 2014.
- Papillary Glandular Sign in large Suprasellar Pilocyctic Astrocytoma. Joyce Mbekeani, Ahmed Al-Khani. Abstract →10<sup>th</sup> Symposium Neuroradiologicum, Istanbul, Turkey



# THE ORGAN TRANSPLANT CENTER



## ORGAN TRANSPLANT CENTER

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**T**he Organ Transplant Center (OTC) has been an established division of KFSH&RC since 2011 to provide world leading transplantation healthcare. Research within the OTC is a collaborative effort with the Research Centre of KFSH&RC which focuses on translational, epidemiological and clinical research in organ conditioning, tissue engineering, tolerance induction, medical and surgical innovations and stem cell research.

**Prof. Dieter Broering, MD, PhD**  
DIRECTOR

The advancement of interdisciplinary research and the development of the Organ Transplant Registry enables the translation of our findings to clinical settings. This could potentially have a significant clinical impact on the improvement of health, quality of life and life expectancy for transplant recipients. Education and research within OTC will help provide optimum care for kidney, liver, lung, pancreas and small bowel transplant patients and donors.



**ORGAN TRANSPLANT CENTER**

**PROJECT TITLE:** Organ Transplant Registry. RAC # 2121 012.

**PRINCIPAL INVESTIGATOR:** Broering D, MD, PhD

**CO-INVESTIGATORS:** Al-Sebayel M, AlAhmadi I, Nizami I, Faiyad A

**PROGRESS:** Ongoing.

**DEPARTMENT OF KIDNEY AND PANCREAS TRANSPLANTATION**

**PROJECT TITLE:** Tuberculosis Post Solid Organ Transplantation, Single Center Retrospective Study. RAC # 2121 074.

**PRINCIPAL INVESTIGATOR:** Aleid H, MD, Almukhaini S

**CO-INVESTIGATORS:** Almukhaini S, Hakami H, Alduraibi F, Altalhi H, Alrajhi A

**PROGRESS:** Completed, Publication Phase.

**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:** Alhuraiji H, Alqaraawi A, Raef H, Altalhi M, Almeshari K, Abdulbaki A, Eldali A, Ali T

**PROGRESS:** Completed, Publication Phase

**PROJECT TITLE:** Acute Kidney Injury in Donors: Recipient's Outcomes. RAC # 2131 014.

**PRINCIPAL INVESTIGATOR:** Ali T, MD

**Co-Investogators:** Altalhi M, Almeshari K, Aleid H, Elgamal H, Dimassi W, Alabbasi A, Shoukri M

**PROGRESS:** Completed, Accepted for Publication in QJM (Oxford Journal).

**PROJECT TITLE:** Diabetes Post Kidney Transplantation Incidence, Risk Factor Outcome. RAC # 2131051.

**PRINCIPAL INVESTIGATOR:** Ali T., MD

**PROGRESS:** Publication.

**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, Alahmadi I, Broering D

**PROGRESS:** Ongoing.

**PROJECT TITLE:** Incidence and Impact of Recurrence of Glomerulonephritis after Kidney Transplantation in Saudi Arabia, Single Center Retrospective Study.

**PRINCIPAL INVESTIGATOR:** Aleid H, Hamad E

**PRINCIPAL INVESTIGATOR:** Alkan A, Alhaj M, Ibrahim I

**PROGRESS:** Ongoing.

**DEPARTMENT OF LIVER AND SMALL BOWEL TRANSPLANTATION & HEPATOBILIARY PANCREATIC SURGERY**

**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

**PROGRESS:** 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, Elsiey H, Alhussaini H, Alsuhaibani H, Alkortas D, Moslmani R, Gaber E, Woodman R

**PROGRESS:** 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, Elsiey H, Tayeb H, Boehnert M, Burkholder J, Woodman R, Algoufi T, Alyami H, Swerky W, Alhussaini H, Faiyad A

**PROGRESS:** Ongoing.

**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, Elsiey H, Hashim A, Hegab B, Jubran A, Alzahrani A, Bazarbashi S, Elsaadany A, Tuli M

**PROGRESS:** 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

**PROGRESS:** Ongoing.

**PROJECT TITLE:** Spontaneous Clearance of Hepatitis C Infection After Liver Replantation. RAC # 2141 051.

**PRINCIPAL INVESTIGATOR:** Elsiey H, MD

**CO-INVESTIGATORS:** Almoutaz H, Alsebayel M, Zakareya T, Mohamed H, Abaalkhail F

**PROGRESS:** 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:** Elsiey H, Albahili H

**PROGRESS:** 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, Elsiey H

**PROGRESS:** Ongoing.

## **LUNG TRANSPLANT UNIT**

**PROJECT TITLE:** Spectrum of Transbronchial Lung Biopsy Findings in Post Lung Transplant Patients and Its Implication on Patient Management: Single Center Experience. RAC # 2131 156.

**PRINCIPAL INVESTIGATOR:** Nizami I, MD

**CO-INVESTIGATORS:** Mohammed S, Akram S, Khan B

**PROGRESS:** Ongoing, Data Collection Phase.

**PROJECT TITLE:** The Prevalence and Possible Risk Factors of Swallowing Abnormalities in Post Lung Transplant Patient. RAC # 2121 120.

**PRINCIPAL INVESTIGATOR:** Nizami I, MD

**CO-INVESTIGATORS:** Hassan A, Akram S

**PROGRESS:** Ongoing, Data Analysis Phase.

**PROJECT TITLE:** Accuracy of Doppler Echocardiographic Estimates of Pulmonary Artery Pressures at the King Faisal Specialist Hospital and Research Centre Riyadh. RAC # 2121 127.

**PRINCIPAL INVESTIGATOR:** Nizami I, MD

**CO-INVESTIGATORS:** Khan B, Akram S

**PROGRESS:** Completed.

**PROJECT TITLE:** The Prevalence of Malnutrition and Obesity and its Effect on the Postoperative Outcome of Lung Transplant Patients. RAC # 2121 065.

**PRINCIPAL INVESTIGATOR:** Nizami I, MD

**CO-INVESTIGATORS:** Khan B

**PROGRESS:** Completed.

**PROJECT TITLE:** The Prevalence and Clinical Significance of Impaired Diffusion Capacity in Post Lung Transplant Patients. RAC # 2121 114.

**PRINCIPAL INVESTIGATOR:** Nizami I, MD

**CO-INVESTIGATORS:** Khan B, Alotaibi T

**PROGRESS:** Completed.

## **PUBLICATIONS – ORIGINAL ARTICLES**

### **DEPARTMENT OF LIVER AND SMALL BOWEL TRANSPLANTATION & HEPATOBILIARY PANCREATIC SURGERY**

- Abaalkhail F, Elsiey H, Alomai A, Alghamdi M, Alalawan A, Almasri N, Alhamoudi W. SASLT practice guidelines for the management of hepatitis B virus. Saudi Association for the Study of Liver Diseases and Transplantation (SASLT). Saudi J Gastroenterology. 2014 Jan-Feb; 20(1):5-25.
- Ibrahim A, Alrobayaan A, Alhassan I, Algarni A, Elsiey H. False Track as an Unexpected Complication of therapeutic Endoscopic Retrograde Cholangio Pancreatography. Ibmosina Journal of Medicine and Biomedical Sciences. 2014 Jan; 6(1):34-37.
- Sterneck M, Settmacher U, Ganten T, Sarrazin C, Speidel N, Broering D, Heyne N, Paulus E, Mertens M, Fischer L. Improvement in gastrointestinal and health-related quality of life outcomes after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in liver transplant recipients. Transplant Proc. 2014 Jan-Feb; 46(1):234-40.
- Saleh Y, Eldeen F, Kamel Y, Kabbani M, Alsebayel M, Broering D. Liver transplant in Budd-Chiari syndrome: a single-center experience in Saudi Arabia. Exp Clin Transplant. 2014 February; 12(1):52-54.
- Alsebayel M, Abaalkhail F, Bahili H, Abdo A, Elsiey H, Elsheikh Y, Hegab B, Kamel Y, Algoufi T, Hassan H, Burdelski M, Abdelfattah M, Attallah K, Mahmood T, Saleh Y, Eldeen F, Broering D. Liver transplantation at KFSHRC: achievement and challenges. Ann Saudi Med. 2014 Mar-Apr; 34(2):103-6.
- Khalaf H, Marwan I, Alsebayel M, Elmeteini M, Hosny A, Abdelwahab M, Amer K, Elshobari M, Kamel R, Alqahtani M, Khan I, Bashir A, Hammoudi S, Smadi S, Khalife M, Faraj W, Bentabak K, Khalfallah T, Hassoun A, Bukrah A, Mustafa I. Status of liver transplantation in the Arab world. Transplant Proc. 2014 April 15; 97(7):722-724.
- Alsebayel M. Donor Organ Shortage Crisis: A Case Study Review of a Financial Incentive-Based System. Transplant Proc. 2014 Jun 24;46(2):2030-2035.
- Elsiey H. Regional Variation in Organ Donation in Saudi Arabia. Transplant Proc. 2014 July-Aug; 46(6):2054-2057.
- Elsiey H. Mortality in Patients with Potential Living Donor Liver Transplantation. Gastroenterology & Hepatology: Open Access. 2014 Aug 11; 1(3):00016.
- Eldeen Z, Alsebayel M. Passing loop technique for portal inflow modulation in liver recipients with partial portal vein thrombosis: a case report. Exp Clin Transplant. 2014 Aug; 12(4):374-376
- Nadeem A, Salahuddin N, Elhazmi A, Joseph M, Bohlega B, Sallam H, Elsheikh Y, Broering D. Chloride-liberal fluids are associated with acute kidney injury after liver transplantation. Critical Care. Nov 2014, 18:625.
- Troisi R, Elsheikh Y, Shagrani M, Broering D. First Fully Laparoscopic Donor Hepatectomy

for Pediatric Liver Transplantation Using the Indocyanine Green Near-Infrared Fluorescence Imaging In the Middle East: A Case Report. *Ann Saudi Med* 2014.

### LUNG TRANSPLANT UNIT

- Nizami I, Khan B, Saleh W, Hussein M. Successful Bilateral Lung Transplantation from a Deceased Donor With Active Mycobacterium Tuberculosis Infection. *Ann Thorac Surg* 2014;97: 109-110.
- Hussein M, Aljehani Y, Nizami I, Saleh W. Successful Management of Bilateral Refractory Chylothorax after Double Lung Transplantation for Lymphangiomyomatosis. *Ann Thorac Med* 2014 Apr-Jun;9(2): 124-126.
- Idrees M, Swiston J, Nizami I, Dallah A, Levy D. Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Medical and surgical management for pulmonary arterial hypertension. *Ann Thorac Med* 2014 July;9: 79-91.

### ABSTRACT PRESENTATIONS

#### DEPARTMENT OF KIDNEY AND PANCREAS TRANSPLANTATION

##### Accepted Abstracts- Oral Presentations

- Ali T, MD, Aleid H, MD. Acute Kidney Injury in Donors: Recipient's Outcomes. World Transplantation Congress, San Francisco, USA, 26-31 July 2014.
- Raza S, MD. Impact of body mass index on renal transplant recipients. Outcome, Single center experience. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Raza S, MD, Aleid H, MD. Incidence and types of malignancy post kidney transplantation in Saudi Arabia. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Aleid H, MD. Tuberculosis Post Solid Organ Transplantation, Single Center Retrospective Study. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Aleid H, MD. A Study of the Pathogenic Role of HCV Infection in the Development Of Post Renal Transplant Diabetes Mellitus. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Aleid H, Raza S, Alahmadi I, Ali T, Khan S, Almeshari K. Incidence and Types of Malignancy Post Kidney Transplantation In Saudi Arabia. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Raza S, MD, Aleid H, MD. Impact of Body Mass Index on Kidney Transplant Recipients' Outcome, Single Centre Experience. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Aleid H, MD. IGRA for the Diagnosis of Latent Tuberculosis in Kidney Transplant Recipients. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Tariq Ali; Wael Dimassi; Hazem Elgamal; Amira Alabassi; Hassan Aleid; Mai Altalhi; Mohamed Shoukri; Khalid Almeshari. Long-term outcome of kidney recipients utilizing kidney from deceased donors with severe AKI. World Transplant Conference 2014, San Francisco, USA, 26-31 July 2014. European Society for Organ Transplantation, Spain, 17-18 October 2014.

##### Accepted Abstracts- Poster Presentations

- Aleid H, MD. Tuberculosis Post Solid Organ Transplantation, Single Center Retrospective Study. World Transplantation Congress, San Francisco, USA, 26-31 July 2014.
- Aleid H, MD. A Study of the Pathogenic Role of HCV Infection in the Development Of Post Renal Transplant Diabetes Mellitus. World Transplantation Congress, San Francisco, USA, 26-31 July 2014. Pan Arab Nephrologist Congress, Dubai, UAE, 10-13 December 2014.

**DEPARTMENT OF LIVER AND SMALL BOWEL  
TRANSPLANTATION & HEPATOBILIARY PANCREATIC  
SURGERY**

**Accepted Abstracts- Oral Presentations**

- Abdelfattah M, MD. An Analysis of Outcome for liver retransplantation in Adults: 12 Years single center experience and first Middle East report. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Abdelfattah M, MD. Liver Transplantation for HCC: Saudi Organ Transplant Center Outcome. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Abdelfattah M, MD. Radio-embolization using Yttrium-90 microspheres as bridging and downstaging treatment for unresectable hepatocellular carcinoma prior to liver transplantation: initial single center experience. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Elsiey H, MD. Graft versus Host Disease after liver transplantation single center experience. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Elsiey H, MD. Spontaneous clearance of hepatitis C infection after liver retransplantation. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Alsebayel M, MD. LDLT Versus DDLT in Relation to MELD. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Elgohary A, MD. Living Liver Donor; The Value of Team Work. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Elsiey H, Ibrahim A, Alsebayel M, Alhamoudi W, Alarieh R, Abaalkhail F. Graft Versus Host Disease After Liver Transplantation. Asian Pacific Association for the Study of Liver (APASL), Brisbane, Australia, on 15 March 2014.
- Shagrani M, Burdelski M., Algoufi T., Alhussaini H, Fayyad A, Alsebayel M, Albahili H, Broering D. Our Experience Of Abo-Incompatible Living Related Liver Transplantation In Children. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Broering D, MD, PhD. Minimally Invasive Living Donor Hepatectomy: Technique and Results. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Abdelfattah M, Broering D. Liver Transplantation for HCC: Saudi Organ Transplant Center Outcome. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Abdelfattah M, Alsebayel M, Alsuhaibani H, Broering D. Radio-Embolization Using Yttrium-90 Microspheres as Bridging and Downstaging Treatment for Unresectable Hepatocellular Carcinoma Prior to Liver Transplantation: Initial Single Center Experience. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Abdelfattah M, Alsebayel M, Broering D. An Analysis of Outcome for Liver Retransplantation in Adults: 12 Years Single Center Experience and First Middle East Report. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Elgohary A, Hegab B, Fayyad A, Elsiey H, Alsebayel M, Broering D. Living Liver Donor; The Value of Team Work. 7<sup>th</sup> International Living Donor Abdominal Organ Transplant Conference, Padua, Italy, 26-27, September 2014.
- Boehnert M, Pediatric Living Related Liver Transplant at KFSH&RC, 7<sup>th</sup> International Conference: Living Donor Abdominal Organ Transplantation, Padua Italy, 26 Sept. 2014.

**Accepted Abstracts- Poster Presentations**

- Shagrani M, Burdelski M, Algoufi T Alhussaini H, Fayad A, Alsebayel M, Albahili H, Broering D. ABO-Incompatible Liver Transplantation in Children: Saudi Single Centre Experience. 2014 Joint International Congress (ILTS, ELITA & LICAGE), London, UK, 4-7 June 2014.
- Elsheikh Y, Albahili H, Alabbad S, Algohary A, Broering D. Laparoscopic Left Lateral Hepatectomy for Living Donor Liver Transplantation in Pediatrics: A Single Centre Experience. 2014 Joint International Congress (ILTS, ELITA & LICAGE), London, UK, 4-7 June 2014.
- Elsheikh Y, Broering D. Laparoscopic Left Lateral Hepatectomy for Living Donor Liver Transplantation in Pediatrics: A Single Centre Experience. 2014 Joint International Congress (ILTS, ELITA & LICAGE), London, UK, 4-7 June 2014
- Elsheikh Y, Albahili H, Rabei M, Algohary A, Hegab B, Shagrani M, Algoufi T, Burdelski M, Alsebayel M, Broering D. Split Liver Transplantation: Single Center Experience At King Faisal Specialist Hospital & Research Centre in Saudi Arabia. 2014 Joint International Congress (ILTS, ELITA & LICAGE), London, UK, 4-7 June 2014.
- Algoufi T, Shagrani M, Fayyad A, Elsheikh Y, Albahili H, Alsebayel M, Broering D. Current Status And Outcome of Pediatric Liver Transplantation: A Saudi Perspective of Recently Established Organ Transplant Center. 2014 Joint International Congress (ILTS, ELITA & LICAGE), London, UK, 4-7 June 2014.
- Elsiesy H, MD. Spontaneous clearance of hepatitis C infection after liver retransplantation. 14<sup>th</sup> Congress of the Middle East Society for Organ Transplantation, Istanbul, Turkey, 10-13 September 2014.
- Elsiesy H, MD. Safety of Right-Lobe living donor liver transplant from donors with Gilbert Syndrome. 1<sup>st</sup> International Congress of LDLT Study Group, Seoul, Korea, 7-8 November 2014.
- Alsebayel M, MD. Cadaveric versus Living Donor Liver Transplant Survival in Relation to MELD Score. AASLD, Massachusetts, USA, 7-11 November 2014.
- Elsiesy H, MD. Severe Anemia with Sofosbuvir based therapy for hepatitis C (HCV) recurrence post liver transplantation on mycophenolate mofetil (MMF). AASLD, Massachusetts, USA, 7-11 November 2014.

**PRESENTATIONS – INVITED SPEAKERS****DEPARTMENT OF KIDNEY AND PANCREAS TRANSPLANTATION**

- Hassan Aleid. Hypertension and kidney disease. Saudi Hypertension Conference, Riyadh 2 April 2014.
- Hassan Aleid. How to promote kidney donation in Saudi Arabia. World Kidney Day Activity, Alhafouf, 17 March 2014

**DEPARTMENT OF LIVER AND SMALL BOWEL TRANSPLANTATION & HEPATOBILIARY PANCREATIC SURGERY**

- ElSiesy H, Refractory Ascites. Dept. of Liver & Small Bowel Transplantation & Hepatobiliary-Pancreatic Surgery Grand Rounds, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, 4 Feb. 2014
- ElSiesy H. Refractory Ascites. Gastro/Hepatology Update Conference, Qatif, 5 February 2014
- Broering D, MD, PhD. Challenges in Split Liver Transplantation. The 2<sup>nd</sup> Liver Diseases & Transplantation Symposium. King Saud Bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Ministry of National Guard-Health Affairs, Riyadh, Saudi Arabia. 19-20 February 2014.
- Shagrani M, MD. ABO-I Liver Transplantation in Children –Single Center Experience. MESOT, Istanbul, Turkey, 11-14 March 2014.
- Al Sebayel M, MD. Role of Surgery in (Resection / Transplant) in HCC. PanArab Interventional Radiology Society, (PAIRS), UAE, Dubai, 6-8 Mar. 2014
- Al Sebayel M, MD. Hepatocellular Carcinoma (HCC) – Clinical Trials. Dept. of Liver & Small Bowel Transplantation & Hepatobiliary-Pancreatic

- Surgery Grand Rounds, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, 14 March 2014.
- Broering D, MD, PhD. Living Related Liver Transplantation: The Saudi Arabia Experience. Emirates Gastroenterology & Hepatology Conference, Dubai, UAE, 3-5 April 2014.
  - ElSiesy H. Updates in Post Liver Transplantation Long Term Care. Emirates Gastroenterology & Hepatology Conference, 3 April 2014.
  - Broering D, MD, PhD. Surgical Therapy of Hilar Cholangiocarcinoma. 9<sup>th</sup> Annual Scientific Congress of Saudi General Surgery Society (SGSS), King Faisal Convention Center, King Abdulaziz University Hospital, Jeddah, Saudi Arabia, 8-10 April 2014.
  - Shagrani M, MD. Use of Rituximab in Antibody mediated rejection status post ABO-I liver transplantation in Pediatric case. Pediatric Hepatology Summer Course (ESPGHAN), Italy, May 2014.
  - Shagrani M, MD. PFIC what we need to know? Maternity Children Hospital, Dammam, Saudi Arabia, May 2014.
  - Broering D, MD, PhD. Surgical Therapy of Hilar Cholangiocarcinoma. Department of Medicine Grand Rounds, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, 06 May 2014
  - Broering D, MD, PhD. Liver Transplantation for HCC: Saudi Organ Transplant Center Outcome. The 3<sup>rd</sup> International Gastrointestinal and Liver Oncology Conference (IGILO), Cairo, Egypt, 15-16 May 2014.
  - Broering D, MD, PhD. Practical Session: "Liver Transplantation Workshop". Member, Experts Working Group. The 3<sup>rd</sup> International Gastrointestinal and Liver Oncology Conference (IGILO), Cairo, Egypt, 15-16 May 2014.
  - Broering D, MD, PhD. Current Status of Organ Transplant at the Organ Transplant Center of KFSH&RC-Riyadh. The 5<sup>th</sup> Jordanian-Romanian Medical Conference and the Third International Romanian Medical Universities Graduates Congress, Amman, Jordan, 28 – 31 May 2014.
  - Broering D, MD, PhD. Indications and Outcome of Liver Transplantation for Children and Adults. Department of Family Medicine & Polyclinic Grand Rounds, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, 09 June 2014.
  - Broering D, MD, PhD. Organ Transplant Center – A Look into the Future. 1<sup>st</sup> KFSH&RC Solid Organ Transplant Nursing Awareness Day, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, 11 June 2014.
  - Broering D, MD, PhD. Organ Transplant Center Road Map: Achievements, Challenges & Resolutions. Department of Surgery Grand Rounds, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, 12 June 2014.
  - Broering D, MD, PhD. Session: 8<sup>th</sup> Basic Course in Split Liver, "Anatomy of the Liver Relevant to Splitting." Master, Practical Session: "Hands-on Course of Ex-Vivo Liver Splitting.". ESOT – 10<sup>th</sup> European Donor Surgery Masterclass & 8<sup>th</sup> Basic Course on the Split Liver. Leiden University Medical Center (LUMC), Department of Human Anatomy, Leiden, The Netherlands, 23-25 June, 2014.
  - Al Sebayel M, MD, Living Donor Liver Transplant vs. Cadaveric Liver Transplant: Single Center Experience in More Than 500 Cases. 14<sup>th</sup> Congress of the MESOT, 11 Sept. 2014, Istanbul, Turkey.
  - Broering D, MD, PhD. Minimally Invasive Donor Hepatectomy. 1<sup>st</sup> Conference of the Egyptian Transplantation Society (ETS), Cairo, Egypt, 17-18 September 2014.
  - Broering D, MD, PhD. Strategies to reduce biliary complications in living donor liver transplantation. 1<sup>st</sup> Conference of the Egyptian Transplantation Society (ETS), Cairo, Egypt, 17-18 September 2014.
  - Broering D, MD, PhD. Surgical Treatment for Colorectal Liver Metastasis: lessons learned from segmental liver transplantation. Keynote Speaker. 3<sup>rd</sup> Colorectal Symposium: Colorectal Cancer and Liver Metastasis Treatment, Doha, Qatar, 16-18 October 2014.
  - AbaAlKhail F. Modern Management of Challenges in GI Practice. 3<sup>rd</sup> Gastroenterology and Hepatology Board Review Course, 22 November 2014

- ElSiesy H. Progressive Familial Intrahepatic Cholestasis. 2<sup>nd</sup> Saudi Association for Study Liver Disease and Transplantation (SASLT), University of Dammam. 27 Nov. 2014.
- Aba AlKhail F. Management of HCV Post Liver Transplantation. 2<sup>nd</sup> Saudi Association for Study Liver Disease and Transplantation (SASLT), 27 Nov. 2014, University of Dammam, 27 November 2014
- Aba AlKhail F. Saudi Guidelines of HCC, General Hospital, Dammam, KSA, 27 November 2014.
- Al Sebayel, M, MD, Legal and Ethical Issues in Liver Transplant, Basic Organ Transplant Course Nursing Affairs, KFSH&RC-RIYADH, 27 Nov. 2014.
- Al Sebayel M, MD. Management of Early Stages of HCC (Resection, Transplantation and RFA) HCC Monometric Symposium, King Fahad Gen. Hospital, Jeddah, 19 Dec. 2014.

#### **LUNG TRANSPLANT UNIT**

- Nizami I, MD. Idiopathic PAH; Diagnosis and management. Speaker 11<sup>th</sup> Biennial International Chest Conference on Chest Diseases and Lung Health, Islamabad, Pakistan, 20 April 2014.

#### **APPROVED GRANTS**

##### **DEPARTMENT OF LIVER AND SMALL BOWEL TRANSPLANTATION & HEPATOBILIARY PANCREATIC SURGERY**

- Alsebayel M, Albahili H, Broering D, Elsheikh Y, Abaalkhail F, Boehnert M. Rescue Therapy Of Retrieved Organs From Deceased Donors: Liver *Ex Vivo* Machine Perfusion. (December 2013).

# THE DEPARTMENT OF PEDIATRICS



## DEPARTMENT OF PEDIATRICS

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**T**he 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 with 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 achievement in 2013. The objective for 2014 is to maintain momentum of trainee involvement in research. This report summarizes RAC approved projects that were initiated, on-going and completed for 2014.

**Prof. Ibrahim Bin-Hussain, MD**  
CHAIRMAN

**Wajeeh Al-Dekhail, MD**  
PEDIATRIC RESEARCH CEOMMITTEE  
CHAIRMAN

**PROJECT TITLE:** Clinical and Molecular Characterization of 3Beta-Hydroxysteroid Dehydrogenase Deficiency in Saudi Patients. (RAC # 2131121).

**INVESTIGATORS:** Afaf Al-Sagheir, Rahma Al-Asmari, Ali Al-Zahrani, Nadia Awni Sakati

**ABSTRACT:** A  $3\beta$ \_HSD deficiency is a rare form of congenital adrenal hyperplasia in which synthesis of all steroid hormones is impaired. It is characterized by salt wasting in early infancy with different degree of ambiguous genitalia depending on the type of genetic mutation. This endocrine disorder is one of the rare disorders in the Kingdom of Saudi Arabia. At KFSH&RC, we have 3 families with  $3\beta$ \_HSD deficiency.

Nowadays, molecular analysis of the gene has made it practical to confirm the diagnosis and study phenotype/genotype correlation.

We intend through chart reviews to gather the clinical, endocrinological and molecular data related to these patients and compare our results to previously published data.

Furthermore, the DNA analysis of the gene and identifying the pathogenic mutation is crucial in understanding the molecular pathogenesis of this rare form of CAH and for genetic counseling. Therefore, we will also study the molecular genetics of the 3 existing families and any other patients that may find by PCR and direct sequencing of the  $3\beta$ \_HSD GENE (HSD3B2).

**AIMS AND OBJECTIVES:**

1. Describe the clinical manifestation of patients with  $3\beta$ \_HSD deficiency of CAH in KSA.
2. Identify the underlying mutation in HSD3B2 gene.

**PROJECT TITLE:** Placement of Transjugular Intrahepatic Portosystemic Shunt in Children (TIPSS) (RAC # 2141003).

**INVESTIGATORS:** Wajeeh Al-Dekhail, Ali Al-Mehaidib, Duaa Al-Romaili, Hamad Al-Suhaibani

**ABSTRACT:** Transjugular intrahepatic portosystemic shunt (TIPSS) is a common procedure used in adult age group. However, it is not commonly reported how efficient TIPSS is in the pediatric age group to the knowledge of our centre. This is a single centre study that takes the consideration of the efficacy of TIPSS in children who are underwent this procedure; measuring the correlation of pre-diagnostic labs and diagnosis and post-procedure complication with the efficacy of TIPSS, based on the patients' follow-up appointments and retrospective results. We included a sample size of 12 children who are below 14 years old and underwent TIPSS for different diagnosis.

**AIM:** The aim is to study the correlation of TIPSS risks and success rate in children with TIPSS, including pre-diagnostic labs, diagnosis and post-procedure follow-up clinical symptoms and signs.

**PROJECT TITLE:** Congenital Hepatic Fibrosis: A Single Centre Experience. (RAC # 2141119).

**INVESTIGATORS:** Wajeeh Al-Dekhail, Ali Al-Mehaidib, Khalid Al-Saleem, Mohammed Banemai, Haifa Al-Awadhi, Ayman Mohamed, Abdulrahman Al-Khateeb

**BACKGROUND:** Congenital hepatic fibrosis (CHF) is an, autosomal recessive, fibrocystic liver disease associated with proliferation of interlobular bile ducts within the portal areas and fibrosis that do not alter hepatic lobular architecture. The fibrosis would affect resistance in portal veins leading to portal hypertension. CHF is known for its variable presentations. It may occur alone, in which case it is called isolated congenital hepatic fibrosis. More frequently, it occurs as a feature of genetic syndromes that also affect such as 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. This is especially true as we explore their geno-phenotype relationship. 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.

**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 cholestatic 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 cholestatic 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.

**HYPOTHESIS AND AIMS:** This case series is expected to provide the following:

1. A description of the clinical presentation and outcome of Saudi Patients diagnosed to have bile acid synthesis disorders along with their specific gene disorders.
2. It will give an update on the most common mutations and trends in Saudi patients presenting to KFSH & RC.
3. 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.

**PROJECT TITLE:** Intrauterine Growth Restriction: Causes and Risk Factors: A Local Experience. (RAC # 2141046).

**INVESTIGATORS:** Saleh Al-Alaiyan, Nora Al-Rumayyan, Abdullah Nour, Ahmad Qudair, Chahdah Skaff

**BACKGROUND:** Intrauterine growth restriction [IUGR] is the term used for a fetus that has not reached its growth potential because of genetic or environmental factors. IUGR results in the birth of an infant who is small for gestational age (SGA) which is most commonly defined as a weight below the 10<sup>th</sup> percentile for the gestational age.(1) At the end of pregnancy, it can result in a low birth weight. Mortality and morbidity are increased in SGA

infants compared with those who are appropriate for gestational age (AGA).(2)

Normal fetal growth reflects the interaction of the fetus's genetically predetermined growth potential and its modulation by the health of the fetus, placenta and the mother. Accurate knowledge of gestational age (GA) is critical to the diagnosis of FGR, given that normal and abnormal fetal size are defined, in part, by comparing the fetal weight of the index fetus to that of other fetuses of the same gestational age.

There are 2 major categories of IUGR: symmetrical and asymmetrical:

- Symmetric FGR, which comprises 20 to 30 percent of growth restricted fetuses, refers to a growth pattern in which all fetal organs are decreased proportionally due to global impairment of early fetal cellular hyperplasia.
- Asymmetric FGR is characterized by a relatively greater decrease in abdominal size than head circumference and is found in the remaining 70 to 80 percent of the IUGR population. There are 2 major categories of IUGR: symmetrical and asymmetrical.(3)

Many different factors cause IUGR, but they may be divided into two large categories based on the etiology. These categories include fetoplacental and maternal factors. Within the categories of maternal and fetoplacental factors are many specific causes. In this study the fetal and placental factors will be analyzed separately.

**AIMS:** The aim of this study is to evaluate the magnitude of perinatal risk factors in causation in KFSH and to compare to appropriate for gestational age infants admitted to the NICU and normal nursery.

**PROJECT TITLE:** Perception of Pediatric Residents in Communication Competences – A Cross Sectional Survey From 13 Hospitals in Saudi Arabia. (RAC # 2131025).

**INVESTIGATORS:** Saleh Al-Alaiyan, Tariq Al-Ofisan, Moath Abdulsalam

**BACKGROUND:** The delivery of quality health care requires effective physician-patient communication. Evidence-based studies show that good communication and focus on the relationship between patient and physician correlate directly with improved quality of care including symptom improvement (Mumford et al. 1982; Uhlmann et al. 1988; Brody et al. 1989; Stewart 1995; Stewart et al. 2000) increased patient adherence to treatment plans (DiMatteo 2004), better management of chronic conditions (Heisler et al. 2002; Gascon et al. 2004; Cabana et al. 2006), increased patient and physician satisfaction (Flocke et al. 2002; Daghigho et al. 2003), and reduced risk of medical errors (Woolf et al. 2004) and malpractice claims (Shapiro et al. 1989; Lester & Smith 1993; Levinson et al. 1997). Physicians' caring and openness to communication are significant factors in patients' deciding to continue a relationship with their physician (DiMatteo et al. 1979; Safran et al. 2001). Communication problems in medical care are common (Tates et al. 2002) and may negatively affect patient management and outcomes. Public sector complaints about physicians usually concern communication problems rather than competency issues (Richards 1991), and the majority of malpractice claims arise from communication errors (Beckman et al. 1994).

The pediatric interview and communication between child, adolescent, parents/caretakers, and pediatrician remain unique. While we can identify general communication skills competencies to teach and how to teach them (Rider & Keefer 2006; Rider 2007), little evidence exists as to which skills are most important for pediatric residents to learn and what content areas should receive emphasis in the curriculum.

**PURPOSE AND AIMS OF THE STUDY:** Residents' self-efficacy or confidence in successfully using communication skills is important, because high self-efficacy is

related to successful use of skills (Smith et al. 1995). Studies show that confidence to perform successfully predicts the use of new skills (Bandura 1983) and actual performance, and that self-efficacy is relevant to medical education (Tresolini & Stritter 1994). Our objective was to examine pediatric residents' (a) attitudes concerning communication skills, (b) perceptions of the importance of developing communication skills, (c) confidence in their own communication skills, and (d) system supports in the pediatric residency program that are relevant to learning and maintaining these skills.

**PROJECT TITLE:** Radiosynovectomy with Yttrium-90 in Camptodactyly-arthropathy-coxa vara-pericarditis syndrome. (RAC # 2141027).

**INVESTIGATORS:** Sulaiman Al-Mayouf, Nora Al-Mutairi, Khalid Alismail

**SUMMARY:** Camptodactyly-arthropathy-coxa-vara-pericarditis (CACP) syndrome is one of the familial arthropathy syndromes. Unfortunately, there is no effective treatment yet. Affected individuals suffer from limited range of motions mainly the large joints, which might interfere with the daily activities. Synovial hyperplasia and loss of the lubricating function is the principal pathological feature of this syndrome. Medical synovectomy (Radiosynovectomy) using radioactive isotope considered as an alternative option. The radioactivity concentrates in the synovium causing necrosis of the proliferating synoviocytes. Radiosynovectomy is a local and minimally invasive radiotherapy for treating variety of chronic inflammatory arthritis such rheumatoid arthritis, osteoarthritis; radiosynovectomy also represents an adjuvant therapy in patients pigmented villonodular synovitis and hemophilic arthropathy. It seems that radiosynovectomy is safe and highly beneficial to children with hemophilic arthropathy. To assess the effectiveness of radiation synovectomy in the treatment of knee arthropathy, using Yttrium-90 in patients with CACP syndrome.

**OBJECTIVE:** The aim of this pilot, clinical study is to assess the effectiveness of radiation synovectomy in the treatment of knee arthropathy, using Yttrium-90 in patients with CACP syndrome.

**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.

#### OBJECTIVES

1. To report the clinical manifestations of JDM children from 3 Arab countries (Saudi Arabia, Jordan, and Oman).
2. To highlight the quality of life and long-term outcomes
3. To compare the results with other cohorts from different ethnicities.

**PROJECT TITLE:** Hepatic Granuloma in Children: A Single Center Experience (RAC # 2131097).

**INVESTIGATORS:** Ali AlMehaidib, Sulaiman AlMayouf, Bassel AlShammari, Halima AlJowder, Hadeel AlManea

**BACKGROUND:** Granuloma is the focal aggregate of epithelioid histiocytes with and without multinucleated giant cells that are usually surrounded by lymphocytes. Many diseases that produce granulomas can involve the liver. Some are intrinsic hepatic diseases, whereas others are disseminated systemic diseases that involve the liver and other organs.

Hepatic granuloma represents a nonspecific reaction to specific antigens and occur in a variety of infectious and noninfectious diseases. They represent a delayed type, specialized, cell-mediated immune response to a wide range of antigenic stimuli. It is also known as a pathological condition that may occur as a result of a wide spectrum of etiologies, requiring a systematic and organized approach for accurate diagnosis and treatment. Morphological characteristics of the granuloma itself, as well as the surrounding liver tissue, its type, localization, and size each play an essential role in the differential diagnosis. The diagnosis of granulomas in the liver is usually made by the histopathologist and requires careful histological evaluation. Common etiologies worldwide include tuberculosis and sarcoidosis; however, noninfectious aetiologies like primary biliary cirrhosis (PBC) form the majority of granulomatous inflammations in the Western world in adult. Previous studies from Saudi Arabia have identified an infectious etiology in up to 96% of adult cases with hepatic granuloma. Generally, the incidence of hepatic granuloma varies from 1 to 14.6% of all liver biopsies whereas this incidence varies with both geographical location and patient population.

In Saudi Arabia we believe that the drop in percentile from 14.6% reaching 1.2 % over period of 18 yrs was partially attributed to the general

improvement in the socioeconomic status of the population and due to the advance in medical therapeutic options.

To the best of our knowledge, the only published study from our region was done in Iran describing the prevalence and etiology of hepatic granuloma in children from a tertiary medical center.

**AIMS AND OBJECTIVES:** Since most of the reviews in Saudi Arabia on the etiology of hepatic granuloma were from adult studies and would not necessarily reflect the experience in pediatrics age group we aim to evaluate the etiology, the clinical, biochemical, radiological presentation, mode of management, and the outcome of the patient who a hepatic granuloma was diagnosed by histopathology of liver biopsy specimens in pediatric age group in our tertiary referral center in the last 10 years.

**PROJECT TITLE:** Screening for Endocrinopathies in Childhood Systemic Lupus Erythematosus (RAC # 2131070).

**INVESTIGATORS:** Suliman Al-Mayouf, Doha Homaidah, Afaf AlSaghier

**ABSTRACT:** Autoimmunity plays a role in many disorders including rheumatic disorders such as Systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis (JIA) as well as other disease entities as celiac disease, type 1 diabetes and thyroiditis. SLE undoubtedly is the best model of autoimmune disorders; it is an inflammatory disorder of autoimmune origin, characterized by autoantibodies production and multi-system involvement. Like other autoimmune diseases, the exact etiology of SLE remains undefined. Patients with autoimmune disorder have a higher probability of being affected by a second autoimmune disorder. Furthermore, autoimmune endocrinopathies might overlap with autoimmune rheumatic diseases

The purpose of this study is to determine the frequency of endocrinopathies in children with SLE.

We will elucidate the impact of endocrinopathies on disease activity and outcome of childhood SLE.

**OBJECTIVE:** The purpose of this study is to determine the frequency of endocrinopathies in children with SLE. We will compare the results from children with SLE with those in children with JIA.

We will elucidate the impact of endocrinopathies on disease activity and outcome of childhood SLE.

**PROJECT TITLE:** Allogeneic Stem Cell Transplantation for Hyper-IgM Syndrome: A Single Center Experience. (RAC # 2131110).

**INVESTIGATORS:** Bandar Al-Saud, Abdulaziz Al-Ghonaum, 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.

**OBJECTIVES:** 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.

**PROJECT TITLE:** Outcome of adults with childhood onset systemic lupus erythematosus in Saudi Arabia: Tertiary Center Experience. (RAC # 2131001).

**INVESTIGATORS:** Suliman Al-Mayouf, Hanan Al Hamzi, A. AlShikh

**ABSTRACT:** The childhood rheumatic diseases are a group of chronic disorders with variable courses, morbidity, and outcomes ranging from complete

remission to long-term disability. Systemic lupus erythematosus is one of the major childhood rheumatic diseases, recent reports showed remarkable improvement of the short-term survival and prognosis in childhood onset systemic lupus erythematosus.

In this study, we will review the outcome of adult patients with childhood onset systemic lupus erythematosus whom followed at King Faisal Specialist Hospital, Riyadh. We hope that this work will help us to highlight the high burden of disease associated with childhood onset SLE and understanding the long term outcome of this disease and to identifying the obstacles comprehensive clinical support for these patients as they transition from pediatric to adult rheumatology care.

To the best of our knowledge, there is no available published data about the long term effect of childhood onset SLE on the adulthood period.

**OBJECTIVES:**

1. To report the social, quality of life and outcome in adult patients with childhood onset SLE.
2. To determine the early predictors of this outcome.

**PROJECT TITLE:** Establishment of Primary Immunodeficiency Disease (PID) Registry at KFSHRC. (RAC # 2081111).

**INVESTIGATORS:** Bander Al Saud, Saleh Al Mohsin, Abdulaziz Al-Ghonaum, Hamoud Al-Mousa, Hasan Al-Dhekri, Hassan Al-Rayes, Amal Al Seraihy, Rand Arnaout, Sulaiman Al-Gazlan, Jawad Afzal, Nazeema Elsayed

**Project progress during the report period:**

- A total of 601 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 during the report period:**

- 80 cases were recruited in total.
- 31 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:** Clinical and Molecular Characterization of Pseudohypoaldosteronism type 1 in Saudi Patients. (RAC # 2130013).

**INVESTIGATORS:** Afaf Al-Sagheir, Azza AlShidani, Ali Al-Zahrani, Manal AlShawi

**ABSTRACT:** Pseudohypoaldosteronism type 1 (PHA1) is a rare monogenic disorder of mineralocorticoid resistance characterized by salt wasting, hyperkalemia, high aldosterone levels, and failure to thrive. Two types of PHA1 have been described. An autosomal recessive form is caused by mutations in the epithelial sodium channel ENaC. It usually present with severe and multiorgan symptoms and the autosomal dominant form of PHA1 is due to mutations in the mineralocorticoid receptor causing milder symptoms confined to the renal tubules. Both of them present in early infancy but the systemic form is a lifelong disease whereas patients with the renal form usually improve by the age of 2-3 years. Patients affected with this disease usually present

with failure to thrive and dehydration associated with hyponatraemia, hyperkalemia and metabolic acidosis. The disease is confirmed by presence of high plasma and urinary aldosterone and high plasma renin levels. Nowadays, molecular analysis of the genes responsible for this disease has become possible.

**RESULTS AND CONCLUSIONS:** We reviewed the files of 14 patients from 9 families. Ten out of the fourteen patients (70%) are from al-sharqia region of Saudi Arabia. All presented in the first week of life with hyperkalemia, hyponatremia and metabolic acidosis. 2 out of 14 had arrhythmias secondary to hyperkalemia. All of them had pulmonary manifestations ranging from asthma-like to CF-like disease. Three had skin manifestations. Eight patient underwent sweat chloride test and it is positive in all of them .the molecular analysis showed that all patients have mutation in the ENAC SCN1A subunit.

**PROJECT TITLE:** Divergent Gender Identity in Three Siblings with 46XX Karyotype and Severely Virilizing Congenital Adrenal Hyperplasia Caused by a Novel CYP11B1 Mutation.

**INVESTIGATOR:** Bassam Bin-Abbas

**AIM:** To describe a conflicting gender identity in three karyotypically female siblings with congenital adrenal hyperplasia (CAH) caused by a novel mutation in CYP11B1 gene, assigned at birth as males and followed up to adulthood.

**Case studies:**

We present 3 siblings (16, 14 and 10 year-old) who were born with severe genital virilization and raised as males. Clinical examination showed Prader IV-V external genitalia with a stretched penile length of 7-11cm. Adrenocorticotrophic hormone (ACTH) stimulation test showed a stimulated 11 deoxycorticosteroid (DOC) level of 12300-18700 ug/L (normal 0-5ug/L). Karyotype was 46 XX and

they had Normal sized uterus and ovaries by pelvic ultrasound. Psychological evaluation of the oldest sibling suggested a female gender identity and she declared herself as female, and female sex was re-assigned after one year of psychosocial adjustment. Psychological assessment for the other 2 siblings as well as a fourth 46XY sibling with the same condition showed a male gender identity; they continued their lives as males without significant difficulties.

**Molecular studies:**

DNA was isolated from peripheral leucocytes. Using PCR and direct sequencing, a novel CYP11B1 mutation was detected. This mutation leads to c.53\_54 T insertion (c.53\_54insT) with frameshift and truncation at c.115 (codon 39) of CYP11B1.

**Conclusion:**

Divergent gender identity was observed in those three severely masculinized 46XX siblings with CAH, carrying the same CYP11B1 mutation and having comparable postnatal and probably prenatal androgen exposure and environmental circumstances. This suggests that the basis of gender identity is more complex than chromosomal, biochemical and genetic constitution

**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 control. 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. 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. 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.

**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.

**PROJECT TITLE:** The Incidence & Prognostic Factors for Chronic Kidney Disease in Methylmalonic Acidemia Patients at KFSH&RC. (RAC # 2121056).

**INVESTIGATORS:** Turki AlShareef, Zuhair Rahbeeni, Abdelmoneim Eldali

**AIM:** To determine the incidence and the prognostic factors for CKD in our MMA population.

**RESULTS AND CONCLUSION:** We were able to identify all patients with MMA that have been followed up in KFSH&RC during the proposed study period. Therefore, we identify those patients who are currently under the follow up by dietary service and we grouped them into two groups for affected & control.

**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

**OVERVIEW:** 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/OBJECTIVES:** The overall objectives of this protocol are to:

1. Compare the effectiveness of echinocandin versus amphotericin B or triazole antifungal therapy for pediatric invasive candidiasis; and
2. Define the incidence of pediatric candidiasis.

The study is still on going and in progress.

### SELECTED ACHIEVEMENTS

1. Paediatrics Clinical Information System (PCIS) is up and working well. This comprehensive database serves as a framework that will provide a rich data source for pediatric clinicians. This will significantly enhance the quality and scope of pediatric research.  
<http://rc.kfshrc.edu.sa/bssc/pcis/index.asp>

2. During the Pediatrics Research Day 2015, a total of 37 abstracts were submitted. 16 were presented for oral presentation.

### RESEARCH PUBLICATIONS

#### FULL PAPERS: (PEER-REVIEWED PUBLICATIONS)

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- Sami Al-Haider, Hassan Al-Shehri. Research Training and Productivity Among Trainees in Residency Training Programs Across Saudi Arabia. PUB # 2140022. Oral Presentation for the 7<sup>th</sup> KFSH&RC Residents' Research Day on 06 February 2014.
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- Wajeeh AlDekhail, Eman Buhamrah, Ali AlMehaidib, Majid Al-Fayyadh, Ahmad AlMuhaideb. Use of Oral budesonide in PLE Patients Post Fontan in A Tertiary Care Center in Saudi Arabia. PUB # 2140034. Poster Presentation for the 7<sup>th</sup> KFSH&RC Residents' Research Day on 06 February 2014.
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- MR Aboud, M de Montalembert, A Fiquet, N Kaddah, A Piga, DC Rees, MC Driscoll, Sami Al-Hajjar, Q Jiang, EA Emini, WC Gruber, A Gurtman, DA Scott. Antibody Persistence After Pneumococcal Conjugate Vaccine (PCV13) in 6-7 Year Old Sickle Cell Disease (SCD) Children Previously Vaccinated With Polysaccharide (PPSV23). PUB # 2140046. Poster Presentation in 9<sup>th</sup> International Symposium on Pneumococci

#### POSTERS / ORAL PRESENTATION:

- Sami Al-Hajjar, Husn Frayha, M Al Hazmi, Reem Batawi, K McIntosh, PE Sax, H Hanhauser, DR

- and Pneumococcal Diseases, scheduled to be on display from March 10-13, 2014.
- Sulaiman Al-Mayouf. Utility of biologic agents in childhood orphan inflammatory diseases. PUB # 2140040. Oral Presentation in 16<sup>th</sup> Asia Pacific League of Associations for Rheumatology, March 31 - April 4, 2014, Cebu City, Philippines. Symposium 5C-Autoimmune diseases in pediatric patients, Thursday, 03 April, 16:00-17:30.
  - Hamoud Al-Mousa. Molecular approach in the diagnosis and management of PIDs. PUB # 2140089. Oral Presentation in the 5<sup>th</sup> International Jordanian Congress of Allergy & Immunology, 28-30 May 2014, Amman, Jordan.
  - Tareq Al-Ayed, Davinia E. Washington, G. Michael Davis. Minimal Exhaled Nitric Oxide Production in the Lower Respiratory Tract of Healthy Children Aged 2-7 Years. PUB # 2140185. Oral Presentation for ISRD & ATS 2014, November 7-9, 2014 Shanghai, P.R. China.
  - Duaa Al-Romaili, Ali Al-Mehaidib, Hamad Al-Suhaibani, Wajeeh Al-Dekhail. Transjugular Intrahepatic Portosystemic Shunt (TIPSS) in Children. PUB # 2140198. Poster presentation for the 5<sup>th</sup> Congress of the European Academy of Paediatric Societies EAPS, October 17-21, 2014, Barcelona, Spain.
  - Wajeeh Al-Dekhail, Eman Buhamrah, Ali Al-Mehaidib, Majid Al-Fayyadh, Ahmad Al-Muhaideb, Khalid AlSaleem. Use of oral budesonide in protein losing enteropathy patients post fontan surgery: A single center experience. PUB # 2140220. Oral Presentation for Asia Pacific Digestive Week 2014 (APDW 2014) on 22-25 November 2014, Bali, Indonesia.



# THE DEPARTMENT OF SURGERY



## DEPARTMENT OF SURGERY

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**D**epartment of Surgery always strives to provide state-of-the-art quality patient care. The primary mission of the Department is to provide the community of the Kingdom of Saudi Arabia with the highest quality of tertiary surgical care for all types of complex diseases in a coordinated and balanced program through clinical practice, teaching and research.

It is the goal of the Department to expand the basic and translational research by ensuring that each of the sections 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.

**Prof. Dieter Broering, MD**  
CHAIRMAN

During the Year 2014, the Department of Surgery 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 Surgery Training Sessions.

In order to promote research awareness and activities, the Department conducted its 13<sup>th</sup> Annual Surgical Research Day, wherein junior staff and new generation of surgeons are exposed to the research environment from the beginning of their career so they can carry it over during their training, post training period and during their practice as senior staff. Other members of the staff are also encouraged to conduct clinical trials, studies, and research projects either individually or in collaboration with other departments.

At the end of 2014, the Department of Surgery has 15 publications, 11 abstracts presented individually and in collaboration with other Departments at KFSH&RC and Internationally. We completed and closed 13 projects this year and 4 new research studies started during this year. Currently there are 8 RAC approved ongoing projects and few waiting for approval from office of research affairs (ORA). These projects included clinical, basic, evidence-based, prospective and retrospective studies, either individually or in collaboration with colleagues, other Departments and with national and International institutions.

## RESEARCH PROJECTS

**PROJECT TITLE:** Impact of Surgery on Stage IV Breast Cancer. RAC Proposal #: 2121052.

**PRINCIPAL INVESTIGATOR:** Mariam Mubarak Al-Selami, Badria Al-Johani

**CO-PRINCIPAL INVESTIGATOR:** Taher Al-Twegieri, Osama Al Malik, Dahish Ajarim, Adher AlSayed, Asma Tulbah, Mohamed AlShabanah, Kausar Suleman

**PROJECT DESCRIPTION:** Traditionally, metastatic breast

cancer is considered to be incurable, and the goals of treatment are the prolongation of life and the palliation or prevention of symptoms. Within this context, it is not surprising that local therapy is not routinely recommended for patients presenting with stage iv diseases and intact primary tumors. Surgery is reserved for patients who develop complications such as bleeding, ulceration, and infection at the primary tumor site, a type of surgery that historically has been described as "toilette" mastectomy.

**PROGRESS:** Completed & Closed.

**PROJECT TITLE:** Retrospective Review of DCIS: Role of Sentinel Lymph Node Biopsy. RAC Proposal #: 2121129.

**PRINCIPAL INVESTIGATOR:** Ahmed Al Ameer, Osama Al Malik  
**CO-PRINCIPAL INVESTIGATOR:** Taher Twegieri, Asma Tulbah, Mohammed AlShabanah, Sahar Al Nafaie

**PROJECT DESCRIPTION:** The role of sentinel lymph node biopsy in ductal carcinoma *in situ*. To study the role of SLNB in our patient population (both screen-detected and clinically detected DCIS).

**PROGRESS:** Completed & Closed.

**PROJECT TITLE:** Riedle's Thyroiditis Case Presentation and Literature Review. RAC Proposal #: 2120207.

**PRINCIPAL INVESTIGATOR:** Ahmed Al-Ameer  
**CO-PRINCIPAL INVESTIGATOR:** Saif Al Sobhi, Hindi Al Hindi, Sahar Al Nafaie

**PROJECT DESCRIPTION:** A rare case of thyroiditis which presented by anterior neck mass and it was Riedle's Thyroiditis. To be aware of this diagnosis when managing patients with thyroid diseases.

**PROGRESS:** Completed & Closed.

**PROJECT TITLE:** Number of Regional Negative Lymph Node Affects Survival in Rectal Cancer Patients Treated for Cure. RAC Proposal #: 2131 017.

**PRINCIPAL INVESTIGATOR:** Al-Wusaibie Ahmed

**CO-PRINCIPAL INVESTIGATOR:** Mohammed Mahfoudh, Abduljabbar Alaa, Ashari Luai, Alhomoud Samar, Alsanea Naser

**COLLABORATORS:** Nasser Al-Sanea, MD

Colorectal Unit, Department of Surgery

**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:**

On going.

**PROJECT TITLE:** Phyllodes Breast Tumors: KFSH&RC Experience. RAC Proposal #: 2131008.

**PRINCIPAL INVESTIGATOR:** Dr. Yousef Al-Alalawi, MD

**CO-PRINCIPAL INVESTIGATOR:** Dr. Osama Al-Malik, MD, Dr. Ihab Anwar, MD, Dr. Asma Tulbah, MD, Dr. Taher Twegieri, MD

**PROJECT DESCRIPTION:** Phyllodes tumors of the breast are rare tumors, accounting for less than 0.5% of all breast tumors. These tumors are comprised of both stromal and epithelial elements; and traditionally they are graded by the use of a set of histologic features into benign, borderline, and malignant subtypes.

Unfortunately, the histologic classification of phyllodes tumors does not reliably predict clinical behavior.

The mainstay of treatment of non-metastatic phyllodes tumors of the breast is complete surgical resection with wide resection margins. Lumpectomy or partial mastectomy is the preferred surgical therapy. However, despite the complete surgical resection, local failure rate may be high; and 22% of malignant tumors may give rise to haematogenous metastases. The most frequent site of distant metastases is the lungs. Several predictive factors of recurrence and metastases have been described in the literature, such as positive surgical margins, increased stromal cellularity, stromal overgrowth, stromal atypia and increased mitotic activity.

**OBJECTIVES**

1. Correlate clinico-pathological and molecular characteristics of the phyllodes tumor with conventional prognosis such as age, stage, positive surgical margins, increased stromal cellularity, stromal overgrowth, stromal atypia and increased mitotic activity.
2. The primary endpoint was 5-year cumulative incidence of phyllodes-specific
3. Events, Disease-related events were defined as: ipsilateral breast recurrence, recurrence in the breast and axilla, and distant metastases.
4. Secondary end-points included 5-year cumulative incidence of specific-phyllodes deaths and overall survival.

**PROGRESS:** On going.

**PROJECT TITLE:** Prognostic Significance of Genetic Alterations in Saudi Colorectal Cancers. RAC Proposal #: 2080030. KACST Project #: 08-MED479-20.

**PRINCIPAL INVESTIGATOR:** Khawla Al-Kuraya

**CO-PRINCIPAL INVESTIGATOR:** Shahab Uddin Khan, Maqbool Ahmed, Abdul Khalid Siraj, Zeenath Jehan, Rong Bu, Jihad Abubaker

**COLLABORATORS:** Nasser Al-Sanea, Fouad Al-Dayel

**PROJECT DESCRIPTION:** Although chromosomal instability pathway and microsatellite instability in colorectal carcinomas (CRC) has been extensively researched in the West, there is a dearth of literature documenting these genetic abnormalities in the Saudi CRC. Recently, we have studied the genomic instability pathways in Saudi CRC and subsequently reported the incidence of PIK3CA mutation and PTEN protein expression in Middle Eastern CRCs. Phosphatidylinositol 3'-kinase (PI3K)/AKT and MAPK pathways are two of the key signaling pathways regulating cell proliferation, differentiation, senescence and apoptosis. Earlier studies have suggested possible relationship between both RAS/RAF/MEK and PI3K/AKT pathways. We will investigate the role of PI3K/AKT, MAPK signaling pathways and EGFR dysregulations in CRC using a large tissue microarray cohort of tumor samples. The studies of specific aim 1 determine the prognostic significance of genetic mutations related to MAPK kinase pathway such as KRAS and BRAF mutations and their potential cross talk with other genetic alterations in PI3K/AKT pathway. The studies of aim 2 will determine the prognostic significance of EGFR alterations in Saudi CRC cases. The studies of aim 3 will investigate the prognostic values of micro RNAs: mir-7, mir-21, and miR-214 in Saudi CRCs.

This project should provide comprehensive view of the clinical implications of different genetic alterations operating in the PI3K/AKT and RAS/RAF/MEK pathways and add to our understanding about the roles by which these genetic alterations influence Saudi CRC tumorigenesis and patient outcome.

**PROGRESS:** Completed & Closed.

**PROJECT TITLE:** The Characteristics of the Learning Curve for Total Mesorectal Excision for Rectal Cancer. RAC Proposal #: 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 to be conducted between 2000 and 2011. Demographics, tumor characteristics, post-operative complications, local recurrence and the survival rate will be retrieved. Multivariate analysis will be performed with the following variables: age, gender, cancer staging, type of surgery, tumor 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 5. Advanced stage of rectal cancer has a high incidence of local recurrence rate 4, 5, 8 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 5, 12. Extraction of twelve or more lymph node after rectal excision improves the tumor staging and this decreases contamination of the staging process 5, 7. 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 1, 4, 5, 11. A male gender with narrow pelvis and advanced tumor stage increase the operative time, difficulty of rectal cancer surgery and total length of hospital stay 13. After rectal surgery 90% of local recurrence is diagnosed within the first 3 years 5. Large tumor size, low rectal tumor and narrow pelvis are associated with urinary dysfunctions 5, 7 and anastomotic leak 14. Morbidity after total mesorectal excision is affected by other factors like co-morbidity as assessed by

the American Society of anesthesiology scale. However; morbidity is increased due to wound infection and malnutrition 13.

**PROGRESS:** Ongoing.

**PROJECT TITLE:** Prognostic Value of Pathologic Complete Response after Neoadjuvant Therapy in Rectal Cancer. RAC Proposal #: 2121069.

**PRINCIPAL INVESTIGATOR:** Mahfoudh Mohammed, Alaa Abduljabbar  
**CO-PRINCIPAL INVESTIGATOR:** Nasser Al Sanea, Samar Al Homoud, Luai Ashari

**PROJECT DESCRIPTION:** A retrospective review of all patients at King Faisal Specialist Hospital & Research Centre Riyadh who underwent preoperative radiotherapy and or chemotherapy for rectal cancer followed by rectal surgery to be conducted between 2000 and 2011. Demographics, tumor characteristics, preoperative chemoradiotherapy, recurrence and the survival rate will be retrieved. Multivariate analysis will be performed with the following variables: age, gender, cancer staging, type of surgery, tumor location, tumor size ,number of retrieved lymph node, neo-adjuvant therapy parameters, adjuvant therapy, operative time, length of hospital stay, and follow up duration. Data will be collected from colorectal data base, ICIS and files of the patients. Ethical privacy principles will be followed.

**PROGRESS:** Ongoing.

**PROJECT TITLE:** Risk Factors for Anastomotic Leakage after Anterior Resection for Rectal Cancer. RAC Proposal #: 2131105.

**PRINCIPAL INVESTIGATOR:** Osama Almosallam, Nasser Al Sanea  
**CO-PRINCIPAL INVESTIGATOR:** Alaa Abduljabbar, Luai Ashari, Mahfoudh Mohammed

**PROJECT DESCRIPTION:** To identify risk factors for anastomotic leakage after curative anterior resection for radiated rectal cancer.

A retrospective review of the Colorectal Database at King Faisal Specialist Hospital & Research Center (KFSH&RC) will be conducted for the period 2001-2011. Inclusion criteria includes all patients who underwent curative anterior resection for rectal cancer. Tumor should be located within 15 cm from the anal verge on rigid proctosigmoidoscopy. Leakage is divided into clinical and radiologic. Both will be evaluated. Demographic data along with patient comorbidities, histopathologic characteristics of the tumors, functional outcome, local recurrence, distant metastasis and survival will be extracted from the paper and electronic records. A  $p < 0.05$  is considered significant. A multivariate and univariate analysis will be utilized to assess the significance of each factor studied.

**PROGRESS:** Ongoing.

**PROJECT TITLE:** Enoxaparin Versus Unfractionated Heparin Followed With Aspirin Venous Thromboembolism Prophylaxis Post Laparoscopic Splenectomy: A Randomized Controlled Study. RAC Proposal #: 2131078

**PRINCIPAL INVESTIGATOR:** Hakeam Hakeam, MS Pharm, BCPS  
**CO-PRINCIPAL INVESTIGATOR:** Shima Al-Khaldi, MBBS, Ihab Anwar, MD, Patrick O'Regan, MD, FRCSC, Dania Bu Ali, MBBS, Alaa Al-Hazmi, MD

**PROJECT DESCRIPTION:** Patients undergoing splenectomy for variable etiologies are considered at high risk for the development of thrombosis at visceral veins (splenic, mesenteric and portal), with an incidence exceeding 22% and a latency period extending beyond 10 days postoperatively. Clinical symptoms of post-splenectomy thrombosis may be insidious, and progression can lead to intestinal infarctions, which could lead to fetal bowel ischemia. No guidelines or consensus has been published advising for the optimum venous thrombosis prophylaxis in patients undergoing splenectomy. This could be attributed to the difficulties in recruiting patients undergoing splenectomy, as it's not a frequently performed surgery, with

variability in surgical techniques. Varieties of venous thrombosis prophylaxis modalities post splenectomy have been reported in literature. Most of which were eluted from a retrospective studies, that lack the control and the homogeneity of the timing of pharmacological prophylaxis administration postoperatively. Also, there is no consistency in these studies regarding thrombosis prophylaxis after discharge from hospital. At our referral, tertiary hospital, no standard protocols for venous thrombosis prophylaxis exist, with a variation in thrombosis prophylaxis approach from surgeon to other. Therefore, we are planning to conduct a study to investigate the efficacy of enoxaparin versus unfractionated heparin prophylaxis in adult patients undergoing laparoscopic splenectomy, aiming to recommend the best venous thrombosis prophylaxis for patients undergoing this surgery.

This is prospective, randomized, controlled study, to be conducted at King Faisal Specialist Hospital & Research Centre (KFSH & RC), Riyadh. After obtaining the approval of the institutional review board, all patients submitted for elective surgical resection of the spleen will be screened for inclusion criteria. Eligible subjects will be randomly allocated to one of the two groups of the study based on the VTE prophylaxis regimen employed. Group number 1, will receive enoxaparin 40 mg (subcutaneously once daily starting within 12-hours after surgery and continued for 21 days thereafter. Group number 2 will receive LDUH 5000 unit subcutaneously every 12 hours starting within 12 hours after surgery till discharge from the hospital. Aspirin 81 mg once daily will be prescribed for patients in group 2 if platelets number increased by 50% from baseline or exceeded  $> 500 \times 10^9/L$  before discharge from hospital and continued till day 30 postoperatively. Sample size of the study is 50 patients, with a suspected recruitment period of 24 months. All patients will undergo ultrasonography for their visceral veins (splenic, mesenteric and portal) on day 2 and 14 postoperatively, searching for asymptomatic and symptomatic venous thrombosis. On day 30 after surgery, all patients will be

reassessed for clinical symptoms of thrombosis as well. The incidence of thrombosis at visceral veins will be compared in each group of the study as primary end point.

**PROGRESS:** Ongoing.

**PROJECT TITLE:** Unravelling the Molecular Link Between Obesity and Breast Cancer: Role of Adipocytes and p16<sup>INK4A</sup>. RAC Proposal #: 2143305.

**PRINCIPAL INVESTIGATOR:** Dr. Abdllilah Aboussekhra, PhD  
**CO-PRINCIPAL INVESTIGATOR:** Huda Al-Khalaf, Asma Tulba, Adher ALSayed, Ihab Anwar, Mohamed Amir Mrad

**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, it 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. We would like to identify the adipokines that are involved and study their effects on mammary cell. In addition, we will study the impact of the tumor suppressor p16 protein in regulating the activity of adipocytes and the secretion of adipokines. We will also apply the xMAP technology to identify key adipocytes genes that are obesity- and breast cancer- related.

The resulting data will provide new insights into the molecular link between obesity and breast cancer and will open up new possibilities for developing preventive as well as therapeutic strategies not

only for breast cancer but for other obesity-related neoplasms.

**PROGRESS:** Ongoing.

**PROJECT TITLE:** Wilm's Tumor and Breast Feeding. RAC Proposal #: 2071004.

**PRINCIPAL INVESTIGATOR:** Saud Al Shanafey  
**CO-PRINCIPAL INVESTIGATOR:** Fawaz Ibrahim, Salman Taghreed

**PROJECT DESCRIPTION:** To check if there is any relation between breast feeding & Wilm's tumor.

**PROGRESS:** Completed & Closed.

**PROJECT TITLE:** Renal Tumors in Infants. RAC Proposal #: 2071009.

**PRINCIPAL INVESTIGATOR:** Saud Al Shanafey  
**CO-PRINCIPAL INVESTIGATOR:** Fawaz Ibrahim

**PROJECT DESCRIPTION:** Simple review of renal tumors in infants, descriptive study.

**PROGRESS:** Completed & Closed.

**PROJECT TITLE:** Persistent Hyperinsulinemic Hypoglycemia of Infancy (Nesidioblastosis): Pathological Stratification. RAC Proposal #: 2071010.

**PRINCIPAL INVESTIGATOR:** Saud Al Shanafey

**PROJECT DESCRIPTION:** Looking at the pathology of patients with Nesidioblastosis and check if it has any input on outcome.

**PROGRESS:** Completed & Closed.

**PROJECT TITLE:** Laparoscopic Liver Biopsy. RAC Proposal #: 2101022.

**PRINCIPAL INVESTIGATOR:** Zakaria Habib  
**CO-PRINCIPAL INVESTIGATOR:** Mila Kolar, Mohammed Banemai

**Tabasum Akram, Hadeel Al Manea**

**PROJECT DESCRIPTION:** Liver biopsy is used frequently in different specialties of pediatrics in order to reach a diagnosis and assess the extent of liver disease and response to medical therapy. Liver biopsy can be obtained by a gastroenterologist, radiologist or a surgeon. The aim of the study is to assess the safety of laparoscopic liver biopsy and to assess the diagnostic yield of laparoscopic liver biopsy.

**PROGRESS:** On hold.

**PROJECT TITLE:** Doudenal Tubular Flap in the Surgical Repair of the Choledochal Cyst. RAC Proposal #: 2120005.

**PRINCIPAL INVESTIGATOR:** Zakaria Habib, Raafat El-Sayed  
**CO-PRINCIPAL INVESTIGATOR:** Mila Kolar

**PROJECT DESCRIPTION:** Choledochal cyst is a congenital cystic dilatation of the extra hepatic biliary tree, usually diagnosed in the childhood. Early treatment can prevent further complications. Duodenal tubular flap – peristaltic or antiperistaltic could prevent complications related with the currently used surgical techniques.

Choledochal cyst is a congenital anomaly. In some types of it is managed surgically by hepatico-duodenostomy, Roux-en-Y hepatico-jejunostomy and replacement by the appendix.

Proposed procedure is a duodenal tubular flap could be peristaltic or antiperistaltic with the advantage of expected to be physiologic with an antireflux mechanism.

Our hypothesis is that duodenal tubular flap as a surgical technique could be better surgical option in the management of the choledochal cyst than the currently used techniques, allowing good bile drainage, preventing cholangitis and bile stone formation.

**PROGRESS:** Completed & Closed.

**PROJECT TITLE:** Surgical Management of Pulmonary Aspergilliosis in Pediatric Population. RAC Proposal #: 2131021.

**PRINCIPAL INVESTIGATOR:** Saud Al-Shanafey

**CO-PRINCIPAL INVESTIGATOR:** Noora Al-Moosa, Ibrahim Bin Hussain, Hindi Al Hindi

**PROJECT DESCRIPTION:** Study about this pathology in children. Data collected, analysed, abstract produced.

**PROGRESS:** Completed & Closed.

**PROJECT TITLE:** Thymectomy in Pediatric Population. RAC Proposal #: 2131022.

**PRINCIPAL INVESTIGATOR:** Saud Al-Shanafey

**CO-PRINCIPAL INVESTIGATOR:** Safi Qutab

**PROJECT DESCRIPTION:** Study about this thymectomy in children at our institution. Data collected, analysed, abstract produced.

**PROGRESS:** Completed & Closed.

**PROJECT TITLE:** Pediatric Invasive Basidiobolomycosis in KFSH&RC – Riyadh, with a Review of Worldwide Cases. RAC Proposal #: 2131008.

**PRINCIPAL INVESTIGATOR:** Ibrahim Bin Hussain

**CO-PRINCIPAL INVESTIGATOR:** Tariq Al Ofisan,

**CO-INVESTIGATOR:** Saud Al-Shanafey, Wajeeh Al Dekhail, Faisal Bin Hussain

**PROJECT DESCRIPTION:** Invasive Basidiobolomycosis is a rare, emerging disease with scattered reported cases in pediatric. We notice there is increase number of cases reported in Saudi Arabia and arid region world wide, suggesting environmental exposure.

Basidiobolomycosis is a manifestation of infection caused by fungus *Basidiobolus ranarum*,

an environmental saprophytic fungus found worldwide in soil, decaying organic mater, and gastrointestinal tracts of amphibians, fish, reptiles, and insectivorous bats. It belongs to the order Entomophthorales, of the class Zygomycetes. Basidiobolomycosis, which is characterized by chronic subcutaneous induration affecting limbs, trunk, and buttocks, originate mostly in tropical area of South America, Africa and Asia.

Minor trauma, local inoculation, and insect bites appear to be the predominant mode of Acquisition.

Visceral involvement with *Basidiobolus* is rare; the first presumed case of gastrointestinal basidiobolomycosis {GIB} was reported in 1964 in a 6 year Nigerian boy (7); in the United States, GIB was first described in 1986 in adult pt (8). Since then, especially in the past three decades, well-documented cases have been reported from arid region worldwide. We notice increase number of pediatric Invasive Basidiobolomycosis {PIB} in Saudi Arabia.

**OBJECTIVES:** To describe this entity more detailed and outline it for better understanding of the disease. Also to increase awareness of health care provider that it is easily missed with the 1<sup>st</sup> presentation of patient.

**PROGRESS:** Ongoing.

**PROJECT TITLE:** The Incidence of Extra Pulmonary Malignant Nodules When Comparing Pre-Operative CT Imaging and Intra Operative Lung Palpation. RAC Proposal #: 2121124.

**PRINCIPAL INVESTIGATOR:** Khalid Al Thagafi

**CO-PRINCIPAL INVESTIGATOR:** Omniyah Al Ashgar, Huda Al Maghrabi, Ameen Al Shehri, Awrad Nasralla, Mohammed Hussein, Waleed Saleh, Khaled Al Kattan,

**PROJECT DESCRIPTION:** To find out the incidence at non imaged pulmonary nodules during thoracotomy for metastatectomy.

In the literature, there is a 30% chance that you will find extra nodule when you open the chest for metastatectomy when compared to pre-operative CT scan of the chest.

In this study, we will try to find out that incidence in King Faisal Specialist Hospital.

**PROGRESS:** Completed & Closed.

**PROJECT TITLE:** Development of Autologous Stem Cell Therapy for Patients With Severe Peripheral Arterial Disease of the Lower Limb – A Phase II Non Randomized Study. RAC Proposal #: 2081021.

**PRINCIPAL INVESTIGATOR:** Dr. Nahar Al Anezi, Dr. Adra,  
**CO-PRINCIPAL INVESTIGATOR:** Dr. AlHumaidan

**PROJECT DESCRIPTION:** Critical limb ischemia is a major health problem. Despite available revascularization modalities ie surgical on angioplasty, up to 40% of those patients end up with major amputation and subsequent disabilities.

In this project, we use autology transplant of (MNCS) derived from either bone marrow or peripheral blood to promote the growth of collateral blood vessels and therefore to improve the symptoms and avoid major amputation.

**PROGRESS:** Completed & Closed.

**PROJECT TITLE:** Phase II Prospective Study of the Clinical Efficacy of Autologous Stem Cell Transplantation in Patients with Critical Limb Ischemia. RAC Proposal #: 2081026.

**PRINCIPAL INVESTIGATOR:** Saad AlGarni  
**CO-PRINCIPAL INVESTIGATOR:** Mohamed Shaltout

**PROJECT DESCRIPTION:** This study is testing the efficacy of stem cell therapy in the treatment of patients with significant peripheral vascular disease who has no choice except amputation or to live with severe rest pain. The idea of this stem cell therapy

is to improve angiogenesis, ie new collateral to carry blood from the proximal arteries to distal diseased limb.

**PROGRESS:** Completed & Closed.

## PUBLICATIONS

### BREAST & ENDOCRINE

- High prevalence of mTOR complex activity can be targeted using Torin2 in papillary thyroid carcinoma. Ahmed M, Hussain AR, Bavi P, Ahmed SO, Al Sobhi SS, Al-Dayel F, Uddin S, Al-Kuraya KS. *Carcinogenesis*. 2014 Jul;35(7):1564-72. doi: 10.1093/carcin/bgu051. Epub 2014 Feb 28.
- Breast stromal fibroblasts from histologically normal surgical margins are pro-carcinogenic. Al-Rakan MA, Colak D, Hendrayani SF, Al-Bakheet A, Al-Mohanna FH, Kaya N, Al-Malik O, Aboussekhra A. *J Pathol*. 2014;231(4):457-65. doi: 10.1002/path.4256.
- Age-specific gene expression signatures for breast tumors and cross-species conserved potential cancer progression markers in young women. Colak D, Nofal A, Albakheet A, Nirmal M, Jeprel H, Eldali A, Al-Tweigeri T, Tulbah A, Ajarim D, Malik OA, Inan MS, Kaya N, Park BH, Bin Amer SM. *PLoS One*. 2014 21;8(5):e63204. doi: 10.1371/journal.pone.0063204.

### COLORECTAL SURGERY

- The obstacles facing scientific and medical publishing in Saudi Arabia. Alsanee N, Al-Ghammas A, Pangan-Menor J, Tejano RV, Al-Bassam N, Duero-Ebora J, Vales JA. *Ann Saudi Med*. 2014 May-Jun;34(3):202-6.
- A very low incidence of BRAF mutations in Middle Eastern colorectal carcinoma. Siraj AK, Bu R, Prabhakaran S, Bavi P, Beg S, Al Hazmi M, Al-Rasheed M, Alobaisi K, Al-Dayel F, Al-Manee H, Al-Sanea N, Uddin S, Al-Kuraya KS. *Mol Cancer*. 2014 Jul 8;13:168.

- The dilemma of the threshold age to start screening for colorectal cancer in Saudi Arabia. Alsanea N. *Saudi J Gastroenterol.* 2014 May-Jun;20 (3):141-2.
- Response to Neoadjuvant Chemoradiation in Rectal Cancer: Time to Consider Risk-Adapted Adjuvant chemotherapy at King Faisal Special Hospital and Research Centre. Ahmed Al Zahrani , Mahfoudh Mohammed, Luai Al Ashari, Alaa Abdul Jabbar ,Samar AL Homoud, Ali Al Jubran, Hadeel Al Manae, Shouki Bazarbashi, Mohammed Mohuiddin, Nasser Al Sanea: *Ann Oncol* (2013) 24 (suppl 4):iv86-iv87. doi: 10.1093/annonc/mdt203.176

#### GENERAL & ONCOLOGY SURGERY

- Effect of Nonparallel Placement of In-Circle Bipolar Radiofrequency Ablation Probes on Volume of Tissue Ablated With Heat Sink. Pillai K, Al-Alem I, Akhter J, Chua TC, Shehata M, Morri. *Surg Innov.* 2014 Jun 27. pii: 1553350614539047. [Epub ahead of print].
- Heat Sink Phenomenon of Bipolar and Monopolar Radiofrequency Ablation Observed Using Polypropylene Tubes for Vessel Simulation. Al-Alem I, Pillai K, Akhter J, Chua TC, Morris DL. *Surg Innov.* 2013 Oct 16;21(3):269-276. [Epub ahead of print].

#### PEDIATRIC SURGERY

- Gastric adenocarcinoma presenting with gastric outlet obstruction in a child. Al-Hussaini A, Alghamdi S, Alsaaran R, Al-Kasim F, Habib Z, Ourfali N. *Case Rep Gastrointest Med.* 2014;2014:527471. doi: 10.1155/2014/527471. Epub 2014 Jan 14.
- Prune belly syndrome with overlapping presentation of partial urorectal septum malformation sequence in a female newborn with absent perineal openings. Farooqui A, AlAqeel A, Habib Z. *Case Rep Surg.* 2014;2014:746323. doi: 10.1155/2014/746323. Epub 2014 Dec 9.

#### PLASTIC SURGERY

- Rare presentation of foot postaxial polydactyly. Rafique A, Arshad A, Abu-Zaid A. *J Foot Ankle Surg.* 2014 May-Jun;53(3):331-4. doi: 10.1053/j.jfas.2013.12.023. Epub 2014 Mar

#### THORACIC SURGERY

- Successful management of bilateral refractory chylothorax after double lung transplantation for lymphangiomyomatosis. Hussein M, Aljehani YM, Nizami I, Saleh W. *Ann Thorac Med.* 2014 Apr;9(2):124-6. doi: 10.4103/1817-1737.128862.
- Successful bilateral lung transplantation from a deceased donor with active Mycobacterium tuberculosis infection. Nizami IY, Khan BJ, Saleh W, Hussein M. *Ann Thorac Surg.* 2014 Apr;97(4):e109-10. doi: 10.1016/j.athoracsur.2013.11.077.
- Missed pulmonary metastasis. Althagafi KT1, Alashgar OA, Almaghrabi HS, Nasralla A, Ahmed MH, Alshehri AM, Saleh WN, Alkattan KM. *Asian Cardiovasc Thorac Ann.* 2014 Feb;22(2):183-6.

#### ABSTRACTS & PRESENTATIONS

##### 14<sup>TH</sup> ANNUAL SURGICAL RESEARCH & RESIDENTS' DAY 27 NOVEMBER 2014, KFSH&RC

- Combined Approach in the Management of Refractory Chylous Ascites in Oncology Patients. Dr. Abdullah Al Khudhayri, Dr. Zakaria Habib, Dr. Samer Koussayer.
- Long term survival after curative treatment for colon cancer in Saudi Arabia. Dr. Reem Al Harbi.
- Colorectal Liver Metastasectomy Benchmark in a Tertiary Center in Saudi Arabia. F. A. Al-alem, R. E. Mattar, A. Alsharabi, F. Alsaif, M. Hassanain.
- Risk Factors for Anastomotic Leakage after Anterior resection for Rectal Cancer. Dr. Osama Al Mosallam, Dr. Nasser Al Sanea, Dr. Alaa Abduljabbar, Dr. Luai Ashari, Dr. Mahfoudh Mohammed.

- Outcome of loop versus divided colostomy in the management of anorectal malformations. Osama Al Mosallam MD, Ali Al Assiri MD, Saud Al Shanafey MD.
- Duodeno-Tubular Flap New Technique of Biliary Tract Reconstruction. Ahmed Qannita, Zakaria Habib, Mila Kolar, Raafat El-Sayed, Asmaa Mohamed Ali, Falah Al Mohana, Mohamed Shoukri.
- Chest Wall Reconstruction: Shift of Paradigm? Mohamed Hussein, Waleed Saleh, Mohamed Abdulrafay, Hassan Robaidi, Mohamed Alamsy, Khaled Kattan, Mahmoud Ashour.
- Intra-Operative Paravertebral Block for Post-Operative Analgesia in Thoracotomy Patient: One Center Experience. Mohammed Alamassi, Mohamed Hussein, Waleed Saleh, Mohamed Abdulrafay, Hassan Robaidi, Mahmoud Ashour
- Phyllodes Breast Tumors: KFSH&RC Experience. Yousef Alalawi, Taher Twegjeri, Osama Al Malik, Ihab Anwar, Asma Tulbah.
- Can Volar Plate Heal to the Tendon Sheath? Walaa Al Dhubaibban, Mohammad Al Qattan, Abdulaziz Al Abdulkarim.
- Impact of Surgery in Stage IV Breast Cancer Patients. Dr. Badria Al Johani

#### RELATED ACTIVITIES

We have the following Training Programs in the Department of Surgery:

#### Two (2) Residency Training Programs

- General Surgery Residency Training Program
  - 24 Residents (KFSH&RC)
  - 9 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

#### SYMPOSIA & WORKSHOPS 2014

- 3<sup>rd</sup> Surgical Basic Review Course. 14-16 April 2014, KFSH&RC.
- 1<sup>st</sup> Joint Conference of the Saudi-International Colorectal Diseases Forum. 16-18 March 2014 Four Seasons Hotel, Riyadh
- 14<sup>th</sup> Annual Surgical Research & Residents' Day. 27 November 2014, KFSH&RC

#### UPCOMING ACTIVITIES 2015

- 4<sup>th</sup> Surgical Basic Review Course. 25-26 February 2015, KFSH&RC
- Saudi-International Colorectal Diseases Forum. 29 March 2015. Four Seasons Hotel, Riyadh
- 15<sup>th</sup> Annual Surgical Research & Residents' Day. 26 November 2015, KFSH&RC



# THE UROLOGY DEPARTMENT



## UROLOGY DEPARTMENT

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**T**he Department of Urology continuously conducted various research projects specifically in the field of Urology and Oncology. On-going research activities primarily focus on bladder/renal cancer management, augmentation cystoplasty (management of urinary bladder dysfunction), Micro TESE, urethral stricture disease and infertility/erectile dysfunction.

**Waleed Al Taweel, MD**  
CHAIRMAN

Two (2) of the research projects were presented during the 14th Annual Surgical Research Day, Post Graduate Auditorium, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia last 06 November 2014.

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 PROJECTS

**PROJECT TITLE AND RAC NO:** Outcome of Bladder Cancer Management, RAC#214 1071.

**INVESTIGATORS:** Mohammed Al Otaibi, MD

**CO-INVESTIGATORS:** Emad Rajih, MD, Mohamed Alawi, MD

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** 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 AND RAC NO:** Outcome of Augmentation Cystoplasty in the Management of Urinary Bladder Dysfunction, RAC#214 1089.

**INVESTIGATORS:** Waleed Al Taweel, MD

**CO-INVESTIGATORS:** Raouf Seyam, MD, Shahbaz Mehmood, MD, Mohammed Alawi, MD

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** 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 detrusor 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 AND RAC NO:** Micro-Dissection Testicular Sperm Extraction (TESE): Largest Saudi Experience at KFSH&RC, RAC#214 1091.

**INVESTIGATORS:** Naif Al Hathal, MD

**CO-INVESTIGATORS:** Noor Junejo, MD, Hamad Alakrash, MD, Abdullah Alfakhri, MD

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** 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 AND RAC NO:** Surgical Outcome of Urethral Stricture Disease Results of Hypospadias in Adults, RAC#213 1102.

**INVESTIGATORS:** Waleed Al Taweel, MD

**CO-INVESTIGATORS:** Alaa Mokhtar Hammad, MD, Noor Junejo, MD, Emad Rajih, MD

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** 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 AND RAC NO:** Transurethral Urethral Resection of Bladder Tumor for Superficial Transitional Carcinoma at KFSH&RC. Ten Year Single Surgeon Experience with Bladder Perforation Management and Outcome, RAC#211 1020.

**INVESTIGATORS:** Hassan Al Zahrani, MD

**CO-INVESTIGATORS:** Abdullah Ghazi, MD

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** Transitional Cell Carcinoma is by far the most common type of bladder cancer. More than 9 out of 10 bladder cancers are this type. The cells from transitional cell carcinomas (TCCs) look like the urothelial cells that line the inside of the bladder.

Urothelial cells also line other parts of the urinary tract, such as the lining of the kidneys (called the renal pelvis), the ureters, and the urethra, so TCCs can also occur in these places. In fact, patients with bladder cancer sometimes have other tumors in the lining of the kidneys, ureters, or urethra. If someone has a cancer in one part of their urinary system, the entire urinary tract needs to be checked for tumors.

In Saudi Arabia, the estimated all newly diagnosed cases of bladder cancer was only 211 in 2006, it is ranked 12<sup>th</sup> in males. KFSH&RC is the main referral center in Saudi Arabia. In 2008, sixty three (63) new cases of bladder cancer were reported in the Hospital registry.

The project aims to review single surgeon experience over the last ten (10) years with bladder perforation during TURBT in a teaching center. It also aims to review the management of bladder perforation and the oncological complication related to perforation "seeding outside the bladder or muscle invasion of superficial one".

**PROJECT TITLE AND RAC NO:** Laparoscopic Nephrectomy: A Single Institutional of Peri Operative and Follow Up Outcomes, RAC#210 1005.

**INVESTIGATORS:** Mohammed Al Otaibi, MD

**CO-INVESTIGATORS:** Waleed Al Khudair, MD, Hassan Al Zahrani, MD, Naif Al Hathal, MD

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** Laparoscopic Nephrectomy provides patients with a safe and effective way to remove a diseased or cancerous kidney. Laparoscopic nephrectomy is a minimally invasive technique, which provides patients with less discomfort and equivalent results when compared to the larger incision required with traditional open surgery. When compared to conventional open surgery, laparoscopic nephrectomy has resulted in significantly less post-operative pain, a shorter hospital stay, earlier return to work and daily activities, a more favorable cosmetic result and outcomes identical to that of open surgery.

The project aims to review the KFSH&RC hospital experience in Laparoscopic Nephrectomy pertaining to perioperative and follow up results. This includes a retrospective chart review study of patients who had Laparoscopic Nephrectomy, Laparoscopic Radica Nephrectomy and Laparoscopic Nephroureterectomy at KFSH&RC from 1995-2009.

**PROJECT TITLE AND RAC NO:** Transitional Cell Carcinoma of the Bladder in a Young Age Group, RAC#209 1085.

**INVESTIGATORS:** Khalid Al Othman, MD

**CO-INVESTIGATORS:** Naif Al Hathal, MD

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** Transitional cell carcinoma (TCC, also urothelial cell carcinoma or UCC) is a type of cancer that typically occurs in the urinary system: the kidney, urinary bladder, and accessory organs. It is the most common type of bladder cancer and cancer of the ureter, urethra, and urachus. It is the second most common type

of kidney cancer, but accounts for only five to 10 percent of all primary renal malignant tumors.

It is among the ten most prevalent tumors in Saudi Arabia. Most of urothelial bladder tumors are superficial and up to 25% of them will progress into muscle invasive disease requiring radical surgery and 10% are metastatic at presentation.

The project aims to identify the probable risk factors, stratify the natural history and outcome of bladder transitional cell carcinoma in pediatric age group and younger adults.

**PROJECT TITLE AND RAC NO:** Long Term Outcome of Renal Cell Carcinoma (RCC) Patients Treated with Radical or Partial Nephrectomy in the Last 12 Years, RAC#209 1063.

**INVESTIGATORS:** Waleed Al Khudair, MD, Raouf Seyam, MD

**CO-INVESTIGATORS:** Mohammed Al Otaibi, MD

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** Renal Cell Carcinoma (RCC) represents almost 85% of newly diagnosed malignancies of the kidney. There is an increase in the rate of renal cell carcinoma from 2.3% to 4.3% yearly. This increase may partially be attributed to early detection through the widespread use of noninvasive imaging techniques. This has also been recognized in our eastern populations. Radical Nephrectomy (RN) has been the gold standard treatment for RCC in the last two (2) decades. However, the risk of renal function deterioration after RN has now been well documented. Consequently, there has been a constant development of Nephron sparing surgery (NSS) to avoid unnecessary nephron waste. The aim of NSS is to preserve renal function, but it carries the risk of local recurrence and possibly metastatic disease. Thus, according to current guidelines NSS is now indicated for RCC less than 4 cm. Disease specific survival rates are similar to RN and NSS in such cases regardless of tumor size. Many reports have argued the effects of surgical approach, surgical margin and adrenal involvement and if affecting the oncological outcomes.

The project aims to establish standards for future comparison we must fully appreciate the efficacy, safety and limitations of both radical and NSS for RCC. Therefore, we will review in our experience and report results for the last twelve (12) years at KFSH&RC and also to determine the cancer control regarding all these variables.

**PROJECT TITLE AND RAC NO:** Microvascular Techniques in Surgery for Infertility and Erectile Dysfunction: Training of the Urology Staff, RAC#208 2001.

**INVESTIGATORS:** Raouf Seyam, MD

**CO-INVESTIGATORS:** Said Kattan, MD

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** The project aims to train urology staff and residents in microvascular techniques to refine the skills in surgeries on the vas deference, epididymis, testes and penis. These surgeries carried out in the clinical setting in our department for infertility and erectile dysfunction.

**PROJECT TITLE AND RAC NO:** Identification of Novel Diagnostic and Prognostic Markers for Bladder Cancer Through Whole Genome Methylation Profiling, RAC#214 0009.

**INVESTIGATORS:** Ahmed Yaqinuddin, MD

**CO-INVESTIGATORS:** Waleed Al Khudair, MD, Hassan Al Zahrani, MD, Mohammed Al Otaibi, MD, Waleed Al Taweel, MD

**PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS:** Urinary bladder cancer is the 2<sup>nd</sup> most common urologic cancer world wide. In Saudi Arabia, the incidence of bladder cancer is rising and is now more frequent than prostate cancer. At present, the diagnosis and monitoring of bladder cancer is largely dependent on cystoscopy and subsequent histological examination of the bladder tissue which is an invasive and expensive procedure. Therefore, there is immense need to develop blood or urine based diagnostic and prognostic markers which can sensitively and specifically detect bladder cancer & can aid in monitoring progression of disease. In this regard, changes in the DNA methylation pattern of genome which are the hallmark of carcinogenesis can be employed to detect free floating tumour DNA in the blood or urine samples of bladder cancer patients. In this study we will investigate genome wide methylation status of CpG islands in the DNA derived from bladder cancer tissues and their respective controls by employing a promoter CpG gene chip array. This will allow us to identify CpG islands which are distinctively methylated in bladder cancer. These CpG islands or methylation markers will subsequently be tested for their ability to detect tumour DNA derived from bladder cancer tissue using blood samples of cancer and control patients. This study will not only help us develop insight into the epigenetic mechanisms involved in bladder cancer, but will also allow us to develop novel diagnostic and prognostic markers to manage bladder cancer effectively.



**NURSING AFFAIRS – NURSING RESEARCH  
DIVISION**



## NURSING AFFAIRS

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Over the past years, Nursing Affairs (NA) has committed to conducting high-quality nursing research that is not only meaningful to staff nurses but also translates into practice change at the point of care at KFSH&RC. The Nursing Research Division is highly committed to achieving these goals and provides continuous support to bedside nurses as they develop research proposals, conduct research, and disseminate their findings both internally and externally. NA strives to ensure a climate of inquiry which is the trigger to continuous practice change. The Nursing Research Council and the Nursing Research Mentorship Program both assure the necessary support for nurses to achieve successful nursing research projects which, impacts the professional development of individual nurses as well as the nursing profession as a discipline

**Teresa Bissen, RN, BSN, MPA**  
ASSISTANT CHIEF

NURSING RESEARCH DIVISION:

**M. Sofia Macedo, RN, BSN,**  
**PGHUM;**

**Abeer Hussain, RN, BSN,**  
**Sarah Hogan, RN, MN.**

During the past year the KFSH&RC nurses have reached research targets never seen previously in Nursing Affairs. The Nursing Research Division had entered into a higher level of research commitment. The collaboration with external agencies, such as the universities and funding bodies has raised the quality of research conducted by nurses at KFSH&RC. With the focus being on high quality research, interdisciplinary collaboration, publication, and the engagement of the staff nurses as Principle Investigators has increased.

As a result of the additional emphasis on implementing of research findings into practice, efforts have centered on providing support to bedside nurses to ensure that a moderate to high level of evidence is integrated into practice improvement projects. Finally, the initiation of a new term of the Nursing Research Council, ensures the addition of new members which is vital to the success of the Council's review process.

### **RAC APPROVED RESEARCH ACTIVITY**

**PROJECT TITLE:** Humidified Oxygen Versus Air for the Treatment of Chemotherapy/Radiation Therapy Induced Mucositis. RAC #2101 084.

**INVESTIGATORS:** Irene Chauke, RN, BSN, Aida Atanante, RN, BSN, Ahmad Amro, RN, BSN,.

**PROJECT DESCRIPTION:** Oncology induced mucositis is a painfully, debilitating side effect for patients undergoing chemotherapy/ radiotherapy. Motivated by a striking clinical observation, in which nurses saw remarkable healing of mouth ulcers in one patient receiving humidified oxygen, the investigators of this study have designed a triple arm, randomized control trial to determine the effectiveness of humidified air versus oxygen in the treatment of oral mucositis.

**PROGRESS AND MAJOR FINDINGS:** Progress report was submitted and approved by the Research office. 75 participants enrolled in the study, the PI aims

to enroll a total of 50 participants during the year 2015.

**PROJECT TITLE:** High-Flow Nasal Cannula Versus Continuous Positive Airway Pressure. RAC #2121 008.

**INVESTIGATORS:** Blazy Varughese, RN, Dip ScN, Noel Yeabra, RN, BSN, Raja Abou Ella, MD, Alomari Mohd, RN, BSN, Nisha Kunjappan, RN, Smitha Varghese, RN, BSN, Sofia Macedo, RN, BSN and Harry Baird.

**PROJECT DESCRIPTION:** Respiratory failure in children after cardiac surgery remains a difficult challenge and is associated with high morbidity, mortality and cost. The use of non-invasive modalities such as nasal continuous positive pressure (NCPAP) and humidified high flow nasal cannula (HHFNC) to support respiratory distress in infants has been encouraged in clinical practice in recent years and has been regarded as a reliable and effective means to avoid the use of prolonged invasive ventilation (Dani & Bertini, 2009). Irrespectively, we are unable to find published research comparing the effect of HHFNC versus NCPAP among infants following heart surgery for congenital heart diseases. The purpose of this study is to compare the effect of humidified high flow nasal cannula versus nasal continuous positive airway pressure as non-invasive ventilation tools to support extubated children with respiratory distress following congenital heart surgery.

**PROGRESS AND MAJOR FINDINGS:** Data collection and data analysis are completed. Preliminary data analysis shows that five (5) of the twenty-two (22) patients that went through NCPAP required re-intubation within 24h compared to one (1) of the twenty-two (22) patients that went through HHFNC (relative risk 5.04, 95% confidence interval, p=0.079). Also, there were no differences between the groups in terms of age (p value=0.296) and days on ventilator (p-value=0.566). However, the patients that went through HHFNC have a significant lower ICU LOS, 11.6±9.47 days compared to the patients on NCPAP, who had an ICU LOS of 22.45±13.45

days ( $p=0.004$ ). In addition, the patients that were on HHFNC, were transferred to floor after 5.1 days of starting the therapy, whereas, the patients on NCPAP were transferred to the floor 11.32 days ( $p=0.004$ ) after starting the NCPAP therapy. Further and thorough analysis is being conducted.

**PROJECT TITLE:** Quality of Life in Saudi Muslims Undergoing Preoperative Radiation Therapy and Curative Surgery for Rectal Cancer With and Without a Stoma: A Mixed Method Study. RAC #2121 031.

**INVESTIGATORS:** Denise Hibbert, RN, MSc, PhD Candidate.

**PROJECT DESCRIPTION:** The aim of this study is to investigate quality of life (QOL) in the Saudi population undergoing curative surgery for rectal cancer, and to compare individuals with and without a stoma. It has been reported that individuals with a stoma have a reduced quality of life compared to those who undergo a surgical anastomosis without a stoma. Systematic reviews of studies have so far failed to conclude this. There are few studies that have looked at QOL in Muslim ostomates, with no consideration of this Saudi population. A mixed methods design will be utilized incorporating both quantitative and qualitative methods. Quantitative QOL data will be collected retrospectively on a cross sectional sample of consenting individuals, identified from stoma therapy and colorectal surgery operating room databases. Quantitative data will also be collected prospectively in a longitudinal fashion, from a cohort of consecutive consenting adult patients attending a colorectal surgery outpatient clinic. A purposive sample of the patients identified from the above mentioned cohort will be studied prospectively and followed in a longitudinal fashion using a qualitative, narrative design.

**PROGRESS AND MAJOR FINDINGS:** The pilot study testing the validity and reliability of the questionnaire was completed in 2013. Data collection is planned for the year of 2015.

**PROJECT TITLE:** Adult Bowel Protocol to Prevent Constipation for Pre and Post-Operative Patients With Brain Tumor. RAC #2121 089.

**INVESTIGATORS:** Shiji Poulose, RN, BSN, Sara Angles, RN, MSN. Graham Binns, RN, BSN, Nancy Pompeo, RN, BSN, Dr. Muna Anani, RN, CDE, PhD, Mohammad AlKhateeb, RN, BSN.

**PROJECT DESCRIPTION:** While there is considerable literature on the causes of neurogenic bowel dysfunction, there are few studies that focus on the practical management of constipation associated with a brain tumor. Also, No specific guidelines and numerical risk assessment instruments pertaining to preventing constipation were found in previous research, also there was no research guidelines available nationally at Saudi Arabia. The signs and symptoms of constipation on a patient with a brain tumor are nausea, vomiting, headache, pain abdomen decreased level of consciousness. Add to this, that straining during defecation associated with constipation may increase the intracranial pressure (ICP), predisposing the patient to signs and symptoms of raised ICP. This raised ICP symptom might conflict the clinical picture and prognosis of brain tumor patients, making the health care professionals consider the brain tumor as the major cause for high ICP. This research study aims to prove the hypothesis that consistent use of standardized bowel preparation protocol for all adult patients with brain tumor preoperative and postoperative supports the patients' quality of life, relieve physical and physiological symptoms such as increase intracranial pressure, decrease level of consciousness, relieve abdominal distention, normal vital signs and improve early ambulation.

**PROGRESS AND MAJOR FINDINGS:** Data collection and data analysis completed. The significant difference between the percentages of constipated subjects without protocol is 87% and the percentage of constipated subjects who received the bowel protocol is 10% and the p value is (0.00001). In our sample the incidence of constipation were less

likely in the prospective arm (10%) compared to 87% in the retrospective arm, and a chi square test shows that the relationship between new bowel protocol and development of constipation in brain tumor population is significant ( $P < 0.001$ ).

Furthermore, the total incidence of constipation in both arms came interestingly close to the incidence documented in the literature. The odds of developing constipation in the retrospective arm were 58.5 (unadjusted OR) times higher than that in the prospective arm.

**PROJECT TITLE:** Identifying Current Discharge Planning Practice at the KFSH&RC Heart Center. RAC #2121 102.

**INVESTIGATORS:** Areej AlNasser, RN, BSN, Aliyah AlQarni, RN, BSN.

**PROJECT DESCRIPTION:** Patient discharge from hospital is a complex and challenging process. It should not be treated as a special event but as part of the patient care plan and should be planned from admission. With the increasing demand for hospital beds, especially for elderly people and patients with chronic diseases, the need for having a smooth discharge process and decreasing the hospital "length of stay" (LOS) is increasing daily and becoming a worldwide concern. The potential resolution would be to have, not only excellent quality care during hospitalization, but a well-planned discharge which would include "multi-disciplinary rounds" (MDR). The MDRs should start from admission, and every patient have an "estimated discharge day" (EDD) recorded within 24hrs of admission. The current discharge process at the Heart Centre is often described as fragmented and unplanned. By conducting this research we hope to gain a better understanding of the Heart Center discharge process, highlight the barriers which may interfere with a better discharge process, and make recommendations to the Heart Centre Administration. Aims of the study are to identify current discharge planning practices of health care

professionals working at the KFSH&RC Heart Centre and assess the barriers in executing a planned discharge planning process. A secondary aim is to measure the number of hours between a discharge order being written and the patient leaving the unit.

**PROGRESS AND MAJOR FINDINGS:** The medical record numbers of the patients discharged from the cardiovascular (CV) division were requested from the Heart Center Research Office 01 January – 30 June 2012. 1321 medical records were reviewed for those patients, and the time from the discharge order written until the patient leaves the unit was collected, as well as the patient length of stay. And categorized into three categories, the first category is green coded referring to the patients who had their discharge medications ordered 24 hours prior to the actual discharge date which is the preferred practice. The second category is yellow coded referring to the patients who had their discharge medications ordered on the same day of discharge (08:00 a.m. to 12:00 p.m.). finally, the third category is red coded referring to the patients who had their discharge medications ordered on the same day of discharge but after 12:00 p.m., the average length of stay (LOS) was calculated and coded with purple and added in the same graphs to detect if it's effected by discharge medication order timing. Cardiovascular Division (CV) includes four Services, Adult Cardiology, Cardiac Intensive Care, Cardiac Surgery, and Pediatric Cardiology, and the patients of the attending services are distributed over five unites (C4, A4, CCU, CVSD, CSICU) where the data was collected based on the attending services.

Aiming to identify the discharge planning practices in the Cardiovascular Division, the discharge medication ordering was used as an indicator and the data is reflected in graphs showing the whole Cardiovascular Division. In addition, each attending service data was reflected in separate graph, and those graphs were shared with the department Heads to reflect their staff commitment to achieve the goal of 24 hours prior patient discharge medication ordering.

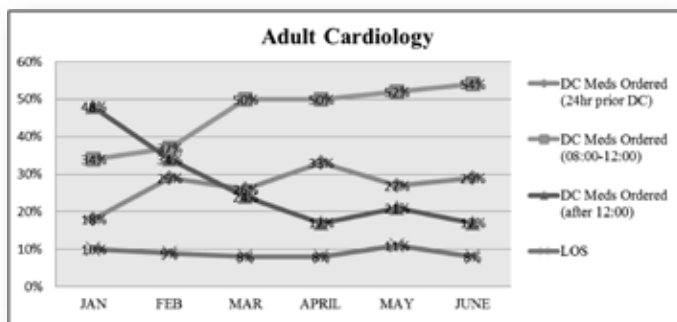


Figure 1. Adult Cardiology Service Discharge Medication order time & Average Length of Stay.

The first service is Adult cardiology having 95 patients discharged in January, their normal practice as it shows in the figure 1, on the month of January was ordering 48% of their patient's discharge medications on the same day of discharge after 12:00 a.m., 34% on the same day of discharge between 08:00 a.m. to 12:00 a.m., only 18% of discharge meds were ordered 24 hour prior discharge, and average length of stay was 10 days.

The management of the Cardiovascular Division started after January to promote for 24 hour prior patient discharge medication ordering and providing the required support to change the discharge practice, and the change is shown in the month of February 95 patients were discharged and the discharge medications ordered on the same day of discharge after 12:00 a.m. decreased to 34%, 37% on the same day of discharge between 08:00 a.m. to 12:00 a.m., discharge meds were ordered 24 hour prior discharge increased to 29%, and the average Length of Stay decreased to 9 days.

In March 110 patients were discharge, the discharge medications ordered on the same day of discharge after 12:00 a.m. decreased to 24%, the same day of discharge between 08:00 a.m. to 12:00 a.m. increased to 50%, discharge meds were ordered 24 hour prior discharge decreased to 26%, and the average Length of Stay decreased to

8 days. Again in April 88 patients were discharged, the discharge medications ordered on the same day of discharge after 12:00 a.m. decreased to 17%, the same day of discharge between 08:00 a.m. to 12:00 a.m. continued to be 50%, discharge meds were ordered 24 hour prior discharge increased to 33%, and the average length of stay remained 8 days.

In May 95 patients were discharged, the discharge medications ordered on the same day of discharge after 12:00 a.m. increase to 21%, the same day of discharge between 08:00 a.m. to 12:00 a.m. increased to 52%, discharge meds were ordered 24 hour prior discharge decreased to 27%, and the average length of stay increase to 11 days but in this month we notice in the data one patient with 105 days LOS a case of heart transplant and the other patient with 156 days LOS a case of aspiration pneumonia, those 2 patients with their high LOS affected the average for the whole service.

Finally for the month of June 106 patients were discharged, the discharge medications ordered on the same day of discharge after 12:00 a.m. decreased again to 17%, the same day of discharge between 08:00 a.m. to 12:00 a.m. increased to 54%, discharge meds were ordered 24 hour prior discharge increased to 29%, and the average length of stay decreased to 8 days.

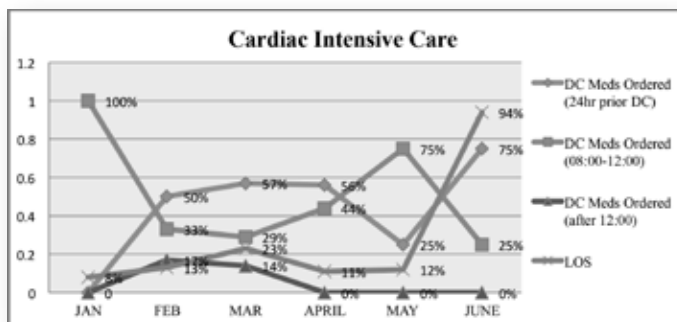


Figure 2. Cardiac Intensive Care Service Discharge Medication order time & Average Length of Stay.

The second service is Cardiac Intensive Care data reflected in figure 2, where the number of patient discharged is not comparable with the other services, since the main practice is to transfer the patients from Intensive care to other units once they are stable.

For January, there was only one patient discharged and the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. so it shows in the graph 100%, and the Average length of stay is 8 days for that patient.

The management of the Cardiovascular Division started after January to promote for 24 hour prior patient discharge medication ordering and providing the required support to change the discharge practice, and the change is shown in the month of February there was 6 patients discharged, the discharge medications ordered on the same day of discharge after 12: 00 a.m. was only 1 patient equal to 17%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. was 33% representing 2 patients, discharge meds were ordered 24 hour prior patient discharge increased to 50% representing 3 patients. And the average length of stay was 13 days.

In March 7 patients were discharged, the discharge medications ordered on the same day of discharge

after 12: 00 a.m. decreased to 14%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. decreased to 29%, discharge meds were ordered 24 hour prior patient discharge increased to 57%, and the average length of stay increased to 23 days since one of the patients was discharged with 106 days length of stay.

In April 9 patients were discharged, the discharge medications ordered on the same day of discharge after 12: 00 a.m. decreased to 0%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. increased to 44%, discharge meds were ordered 24 hour prior patient discharge remains at 56%. And the average length of stay decreases to 11 days.

In May only 4 patients discharged, the discharge medications ordered on the same day of discharge after 12: 00 a.m. persisted at 0%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. increased to 75%, discharge meds were ordered 24 hour prior patient discharge decrease to 25%, and the average length of stay increase to 12 days.

Finally in June 4 patients were discharged, the discharge medications ordered on the same day of discharge after 12: 00 a.m. persisted at 0%, the discharge medications were ordered the same day

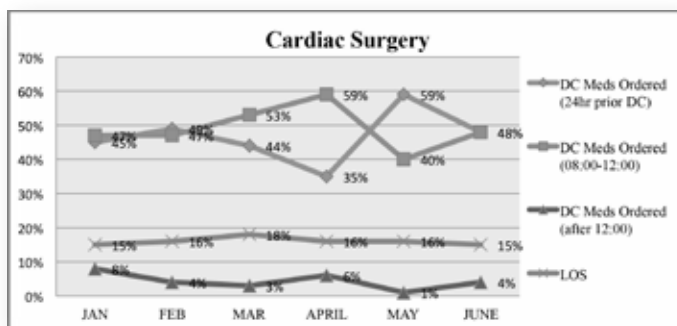


Figure 3. Cardiac Surgery Service Discharge Medication order time & Average Length of Stay.

of discharge between 08: 00 a.m. to 12: 00 a.m. decreased to 25%, discharge meds were ordered 24 hour prior Patient discharge increased to 75%, and the average length of stay increased to 94 days due to the discharge of one patient with 342 days length of stay that affected the average of the whole services.

Cardiac Surgery Service had 72 patients discharged in the month of January and the data reflected in Figure 3, the discharge medications ordered on the same day of discharge after 12: 00 a.m. was 8%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. was 47%, discharge meds were ordered 24 hour prior Patient discharge was 45%, and the Average length of stay is 15 days.

The management of the Cardiovascular Division started after January to promote for 24 hour prior patient discharge medication ordering and providing the required support to change the discharge practice, and the change is shown in the month of February 72 patients were discharged, the discharge medications ordered on the same day of discharge after 12: 00 a.m. decreased to 4%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. remain at 47%, discharge meds were ordered 24 hour prior Patient discharge increase to 49%, and the average length of stay increased to 16 days.

In March 70 patients, the discharge medications ordered on the same day of discharge after 12: 00 a.m. decreased to 3%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. increased to 53%, discharge meds were ordered 24 hour prior Patient discharge decreased to 44%, and the average length of stay increased to 18 days.

In April 69 patients were discharged, the discharge medications ordered on the same day of discharge after 12: 00 a.m. increased to 6%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. increased to 59%, discharge meds were ordered 24 hour prior Patient discharge decreased to 35%, and the average length of stay decreased to 16 days.

In May 73 patients were discharged, the discharge medications ordered on the same day of discharge after 12: 00 a.m. decreased to 1%, the discharge medications were ordered the same day of discharge between

08: 00 a.m. to 12: 00 a.m. decreased to 40%, discharge meds were ordered 24 hour prior Patient discharge increased to 59%, and the average length of stay remained at 16 days.

Finally in June 82 patients were discharged, the discharge medications ordered on the same day

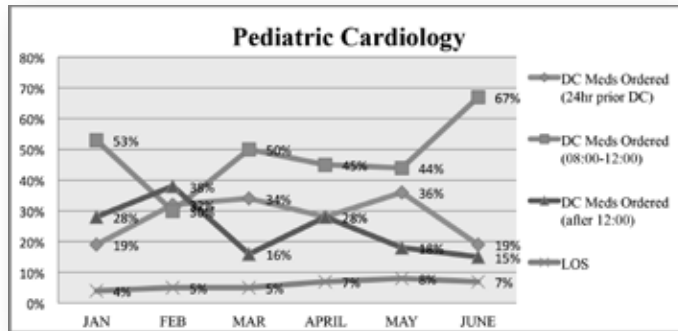


Figure4. Pediatric Cardiology Service Discharge Medication order time & Average Length of Stay.

of discharge after 12: 00 a.m. increased to 4%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. increased to 48%, discharge meds were ordered 24 hour prior Patient discharge decreased to 48%, and the average length of stay decreased to 15 days.

The Pediatric Cardiology Service have 32 patients discharged in January and the data as reflected in figure 4, for the discharge medications ordered on the same day of discharge after 12: 00 a.m. is 28%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. is 53%, discharge meds were ordered 24 hour prior Patient discharge is 19%, and the average length of stay is 4 days.

The management of the Cardiovascular Division started after January to promote for 24 hour prior patient discharge medication ordering and providing the required support to change the discharge practice, but the change did not show in the month of February 34 patients were discharged, the discharge medications ordered on the same day of discharge after 12: 00 a.m. increased to 38%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. decreased to 30%, discharge meds were ordered 24 hour prior Patient discharge increased to 32%, and the average length of stay increased

to 5 days.

In March 32 patients were discharged, the discharge medications ordered on the same day of discharge after 12: 00 a.m. decreased to 16%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. increased to 50%, discharge meds were ordered 24 hour prior Patient discharge increased to 34%, and the average length of stay remain at 5 days.

In April 29 patients were discharged, the discharge medications ordered on the same day of discharge after 12: 00 a.m. increased to 27.5%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. decreased to 45%, discharge meds were ordered 24 hour prior Patient discharge decreased to 27.5%, and the average length of stay increased to 7 days.

In May 22 patients were discharged, the discharge medications ordered on the same day of discharge after 12: 00 a.m. decreased to 18%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. decreased to 44%, discharge meds were ordered 24 hour prior Patient discharge increased to 36%, and the average length of stay increased to 8 days.

Finally in Jun 27 patients were discharged, the

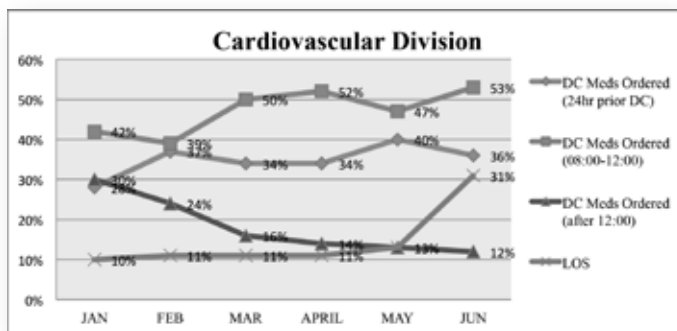


Figure 5. Cardiovascular Division Discharge Medication order time & Average Length of Stay.

discharge medications ordered on the same day of discharge after 12: 00 a.m. decreased to 15%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. increased to 67%, discharge meds were ordered 24 hour prior Patient discharge decreased to 19%, and the average length of stay decreased to 7 days.

Subsequently, the data for all the services was gathered to show the Cardiovascular Division report showing how each service results could affect the whole division. Starting with January, the discharge medications ordered on the same day of discharge after 12: 00 a.m. was 30%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. was 42%, discharge meds were ordered 24 hour prior Patient discharge was 28%, and the average length of stay was 10 days.

The management of the Cardiovascular Division started after January to promote for 24 hour prior patient discharge medication ordering and providing the required support to change the discharge practice, and the change were shown in the month of February, the discharge medications ordered on the same day of discharge after 12: 00 a.m. decreased to 24%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. decreased to 39%,

discharge meds were ordered 24 hour prior Patient discharge increased to 37%, and the average length of stay increased to 11 days.

In March, the discharge medications ordered on the same day of discharge after 12: 00 a.m. decreased to 16%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. increased to 50%, discharge meds were ordered 24 hour prior Patient discharge decreased to 34%, and the average length of increased to 11 days.

In April, the discharge medications ordered on the same day of discharge after 12: 00 a.m. decreased to 14%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. increased to 52%, discharge meds were ordered 24 hour prior Patient discharge remained at 34%, and the average length of stay remained at 11 days.

In May, the discharge medications ordered on the same day of discharge after 12: 00 a.m. decreased to 13%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. decreased to 47%, discharge meds were ordered 24 hour prior Patient discharge increased to 40%, and the average length of stay increased to 13 days.

Finally in Jun, the discharge medications ordered on the same day of discharge after 12: 00 a.m. decreased to 12%, the discharge medications were ordered the same day of discharge between 08: 00 a.m. to 12: 00 a.m. increased to 53%, discharge meds were ordered 24 hour prior Patient discharge decreased to 36%, and the average length of stay increased to 31 days and that is reflecting the increased average length of stay Cardiac Intensive Care services as shown in Figure 5.

**PROJECT TITLE:** Incidence and Risk Factors for Stomal and Peristomal Complications in Patients Referred to in a Tertiary Referral in Saudi Arabia. RAC #2121 117

**INVESTIGATORS:** Denise Hibbert, RN, BSc (Hons), MSc

**PROJECT DESCRIPTION:** Stomal and peristomal complications are reported to reduce quality of life and increase financial burden. Internationally the incidence of stomal and peristomal complications is reported to range from 10-70%, reports from Saudi Arabia are lacking. The aims of this study are to identify the incidence of stomal and peristomal complications and the associated risk factor in patients with incontinent fecal and urinary abdominal stomas. An observational longitudinal design will be utilized. Data pertaining to the stoma, the surgery, and patient characteristics will be obtained from the stoma therapy database.

**PROGRESS AND MAJOR FINDINGS:** The study is in data analysis phase.

**PROJECT TITLE:** Staff Nurses' Perception on Leadership Styles in a Saudi Arabian Hospital. RAC #2121 130.

**INVESTIGATORS:** Ahmed AlKhaibary, RN, BSN, Sultan AlKhaibary, RN, BSN

**PROJECT DESCRIPTION:** The topic of leadership has received much attention especially in nursing

management considering that nurses constitute the largest human resource element in healthcare organizations, and therefore have a great impact on quality of care, patient and staff outcomes. With a worldwide shortage of nurses in the workforce and high rates of turnover among nurses, nurse managers with effective leadership skills are an essential component to the solution for ending the undesirable pattern (Cowden, Cummings & Profetto-McGrath, 2011). This study aims to determine the perception of staff nurses in Saudi Arabia on leadership styles in terms of transformational, transactional and laissez-faire and its impact on organizational outcomes on the aspects of extra effort, organizational commitment and satisfaction of staff utilizing the Multi-Factor Leadership Questionnaire by Avolio and Bass (2000). The study goal is to establish a correlation between the mentioned variables.

**PROGRESS AND MAJOR FINDINGS:** Transformational leadership was employed fairly often ( $M=2.78$ ), transactional leadership sometimes ( $M=2.33$ ) and Laissez-Faire once in a while ( $M=1.44$ ). The leadership outcomes were perceived fairly often (extra effort [ $M=2.68$ ]; effectiveness [ $M=2.91$ ]; satisfaction [ $M=2.97$ ]). Controlling for the characteristics of the staff nurses, Transformational leadership by Transactional Leadership by Laissez-Faire interaction have significant marginal effect on effectiveness ( $F_{2,412}$ ,  $df_6$ ;  $p=.028$ ; partial  $\eta^2=.066$ ) and satisfaction ( $F_{3,034}$ ,  $df_6$ ;  $p=.007$ ; partial  $\eta^2=.081$ ).

**CONCLUSION:** Nurse Managers in this organization were effective in employing Transformational Leadership and Contingent Reward. They were able to shape positive behaviors of staff nurses resulting into the achievement of personal and organizational goals.

**PUBLICATION:** Ahmad E. Aboshaiqah, Ayman M. Hamdan-Mansour, Dennis R. Sherrod, Ahmed Alkhaibary, and Sultan Alkhaibary, "Nurses' Perception of Managers' Leadership Styles and Its Associated Outcomes." American Journal of

Nursing Research, vol. 2, no. 4 (2014): 57-62. doi: 10.12691/ajnr-2-4-1.

**PROJECT TITLE:** Knowledge and Attitude of Nurses in Saudi Arabia Towards Palliative Care. RAC #2121 134.

**INVESTIGATORS:** Gassan Adnan Abudari, RN, BSN, Hassan Zahreddine, Mohammad Alassi, Sania Emara, Hassan Hazeim

**PROJECT DESCRIPTION:** The literature suggests that nurses lack the knowledge and attitude required to care for patients at the end of life. Additionally palliative care is not well recognized as a specialty in the Arab world; as a result many patients are denied appropriate end of life care. This study aims to assess the knowledge and attitude of nurses working at a tertiary care organization in Saudi Arabia towards palliative care, while examining how demographic variables influence nurses' attitude toward caring for terminally ill persons and their families. Data will be collected in a self-administrated questionnaire consisting of demographical data, the palliative care quiz for nurses (PCQN) and the Frommelt Attitude toward Care of the Dying scale (FATCOD). Statistical analysis software (SAS) will be utilized for data analysis.

**PROGRESS AND MAJOR FINDINGS:** In the analysis nurses scored a mean of 112 out of 150 on the FATCOD scale, which is considered a low score when compared to similar studies done in the west, indicating a less positive attitude towards palliative care. The mean score for the PCQN was 9.1 out of 20, which indicates a knowledge deficit of palliative care issues. Conclusion: Results indicate a palliative care knowledge deficit among nurses working at a tertiary care facility in Saudi Arabia. An educational program would allow nurses to foster a more positive attitude towards end of life care, while enhancing their knowledge and skills. our study indicate the needs for further palliative care education program at the hospital level, this educational program should be feasible for providing high quality, well

design and culturally sensitive like end of life nursing education program (ELNEC). - Saudi nurses scored a modest score in both PCQN and FATCOD, high reflect the urgent need for better palliative care integration throughout the health care system, and to begin a comprehensive educational program about palliative care in nursing schools and postgraduate. In this study we have investigated the factors which can influence the level of knowledge and attitude towards palliative care like: age, level of education, palliative care training and years of experience. Nurses with palliative care training and experience scored significantly higher than the nurses who don't have experience and training, however more investigation needed about the nature of palliative care experience and training, since the mean score for PCQN and FATCOD consider low in comparison with other studies done earlier.

**PUBLICATION:** Gassan Abudari, Hassan Zahreddine, Hassan Hazeim, Mohammad Al Assi, Sania Emara. "Knowledge of and attitudes towards palliative care among multinational nurses in Saudi Arabia" International Journal of Palliative Nursing. 2014, Vol 20, No 9.

**PROJECT TITLE:** What is the Impact of a Family Centered Care in Improving Patient Outcome in a Surgical Intensive Care Unit. RAC #2121 135.

**INVESTIGATORS:** Rezaq AlMowaled, RN, BSN, Yousef AlEnazi, RN, BSN

**PROJECT DESCRIPTION:** A family's ability to support the patient may become compromised by their own psychological distress. Thus, to promote optimal outcomes for patient and family, a vital responsibility of the multidisciplinary team is to address the needs and concerns of family members during ICU hospitalization. This study is a prospective cross sectional quantitative study. It will be applied to all the families of adult patients who are admitted in a surgical ICU at King Faisal Specialist Hospital and Research Center – Riyadh, (KFSH&RC), for more than 24 hrs.

The data will be collected by applying a questionnaire which will be distributed to surgical ICU (KFSH&RC) patient's families and for the patient's families who are not able to read or write, we will explain and complete the questionnaire with them.

**PROGRESS AND MAJOR FINDINGS:** This research has raised awareness and the needs of patient's family in ICU. The research also addressed the need of change the structure of ICU to suit the needs for patient's family. The family stated clearly that they need to have explanation of the environment before going into the intensive care unit for the first time. This research addressed the critical needs of family to have specific staff for supporting family's needs at all the time as well as to have specific person to contact at the hospital when unable to visit.

In regard to helping the health care provider at bedside with physical care; most of family agreed to help with patient's physical care. This research addressed the need of patient's family to have waiting room near the patient. As well as this research noticed the need of religion man availability. Clearly more research is needed to produce the evidence for practices in the family centered care in intensive care unit.

**PROJECT TITLE:** What are the Factors Impacting the Effective Utilization of the Discharge Lounge at King Faisal Specialist Hospital & Research Centre, Riyadh. RAC #2121 137.

**INVESTIGATORS:** Aisha Awaji, RN, BSN, Karemah AlRabghi, RN, BSN

**PROJECT DESCRIPTION:** "The discharge lounge is to house patients who are ready to leave the hospital facility while waiting for their transportation to arrive", waiting for the discharge medication, flight ticket, and home supply. (AHC Media LLC FEB 2009)

According to King Faisal Specialist Hospital & Research Centre (KFSH&RC) statistical data, in

regards to the discharge lounge utilization, the discharge lounge area was not effectively utilized and the number of patients who visit the discharge lounge is below the expectation.

Our aim is to explore the contributing factors that impact the effective utilization of discharge lounge from the patient's perspective; this understanding may help the managers to improve the concept of the discharge lounge and therefore increase bed availability for patients who are waiting for admission through Emergency department (DEM).

**PROGRESS AND MAJOR FINDINGS:** Data collection interrupted due to discharge lounge closure for renovations. Once discharge lounge re-opens, data collection will recommence for an expected completion in 2014.

**PROJECT TITLE:** Concern and Coping Strategy of Parents Toward the Leukemic Children in Riyadh, KSA. RAC #2121 138.

**INVESTIGATORS:** Sanaa Alenazi, RN, BSN

**PROJECT DESCRIPTION:** Leukemia is a problematic condition affecting both the patient and the family. When parents faced by their child's diagnosis of leukemia, their reaction of concern and shock may affect their proactivity and understanding of services available. Therefore this may hinder the management and care of these children.

Hence a study into the concern and coping strategies of parents having leukemic children may be of benefit to facilitate nursing care. It may also benefit the facilitation of nursing management and care of leukemia child by his/her parents.

The aims of this study are to assess concerns and coping strategies of Saudi parents towards their leukemic children in Riyadh city by 1). Identify the positive and negative coping strategies of Saudi parents during the disease process and treatment, 2). Detect healthy and non-healthy coping strategies

of Saudi parents during the disease process and treatment stage, 3). Compare father and mother concerns and coping strategies, and 4). Determine cultural factors impeding or facilitating Saudi parents' coping strategies.

**PROGRESS AND MAJOR FINDINGS:** Majority of parents were from King Faisal Special Hospital equal to (70%) compared to Medical City hospital were present by (30%).

The study shows the distribution of leukemic children by region of Kingdom of Saudi Arabia. From this figure the researcher observes that the majority of subjects from outside of Riyadh mainly from west of K.S.A as reflected by 39.32%, from Asier region was 24.16% and the rest of the subject were spread in over the regions in kingdom of Saudi Arabia.

The distribution of parents represented by departments, Was from inpatient 54.44 % compared to 45.56 % From out-patient department.

The percentage of fathers equal to mothers in my subject was 41.9 % to 58.1 % respect. 33.33% of parents presented in range of age at 26-35 years.

From the study, The significant relations were as following:

It was found a significant relation between parents' concern and:

1. Region by (X<sup>2</sup> Test 0.028): if region far they more concerns have.
2. Income by (X<sup>2</sup> Test 0.017): if the income inadequate they had more concerns.

And between daily and weekly coping style for parent's and:

1. Income by (X<sup>2</sup> Test 0.0015): if income inadequate they are less doing daily and weekly coping style.
2. Relation of parent to child by (X<sup>2</sup> Test 0.001):

mothers less doing daily and weekly coping style.

3. Education of parents by (P –value 0.019): if parent's educated they more applied coping style.

And concern of parent about mental health and:

1. Culture value (X<sup>2</sup> Test 0.0015): if the parent practice their culture value less concerns about mental health
2. Contribute to formal hospital committee (X<sup>2</sup> Test 0.04) and join informal committee support resources (X<sup>2</sup> Test 0.): the less parent attend to committee they had more concern about mental health.

**PROJECT TITLE:** Overcoming the Language Barriers in the Intensive Care Unit of King Faisal Specialist Hospital and Research Centre. RAC #2131 055

**INVESTIGATORS:** Shazia Arif, RN, BSN, Shirin Badruddin, RN, BSN

**PROJECT DESCRIPTION:** The mission of the King Faisal Hospital and Research Center is to provide safe and effective care to patients and their families (King Faisal Specialist Hospital and Research Centre Website, 2013). Being accredited by the Joint Commission International Accreditation and planning to get Magnet designation, communication is considered as an important area for patient safety (Joint Commission Accreditation Standards for Hospital, 2010). The patients admitted in this hospital communicate in Arabic language. Health care workers who work here are from different nationalities. Nurses are the ones who are closer to the patient. Statistics showed that staff nurses from 38 different nationalities are hired to work in King Faisal Specialist Hospital and Research Centre (KFSH&RC) with 900 beds (Admission data, 2012). In the intensive care unit, when these new nurses arrive, their grasp of Arabic is limited. The staff nurses utilize the help of the interpreters or the family members to establish a care plan for the

patient; this method does not maintain the patient’s confidentiality or privacy.

The purpose of this study is to focus on the importance of implementing a communication toolkit to enhance the communication between the nurse and the patient. Moreover, this study attempted to evaluate the efficacy of this communication tool prepared for non-Arabic health care providers.

Qualitative and Quantitative pre and post-test study design will be used in this study.

**PROGRESS AND MAJOR FINDINGS:**

A total of 73 participants were enrolled in the study. Only one participant left the study. 72 nurses filled the pre and post questionnaires.

QUESTIONNAIRE STATUS		
Questionnaire	Frequency	Percent
Pre	72	50.0
Post	72	50.0
Total	144	100.0

**Demographic Data**

Majority (32%) of the participants enrolled were from SSCU-B and less were enrolled from MICU D/E (see Table 1.1). 89 percent of the nurses recruiting were female. Participant’s ages varies from 25 to 60 years. Most of the participants (62%) were around 26 to 40 years of age. Their education level was diploma and bachelors. 68% of nurses with bachelors degree were the part of this study. None of the participants were from gulf region. All of the participants were outside Gulf region. Majority of the nurses were from Asian countries and few were from Western countries (see Table 1.2).

90 percent of the nurses did not study Arabic prior coming to King Faisal Specialist Hospital and Research Center. Only 10 percent of the nurses study little Arabic prior coming to this hospital. The results of the study showed that 98% of the nurses

highlighted that language plays an important role while caring for the patient.

**Table 1. Unit Status**

UNIT	PERCENT
SSCUB	32.6
MICU C	19.4
MICU D/E	12.5
CCU	16.0
CSICU	19.4
Total	100.0

**Table 2. Nurses nationality**

COUNTRY	PERCENT
USA	4.9
Canada	11.8
Pakistan	11.8
India	14.6
Malaysia	18.1
South Africa	2.1
UK	4.9
Philippines	22.2
Portugal	2.8
Ireland	1.4
Czech republic	3.5
New Zealand	1.4
Total	100.0

**Level of Comfort ability while Speaking Arabic**

As shown in Table 1.3, only 39 percent were comfortable while caring with Arabic patient and 38 percent ranked their fluency as poor, 41 percent as fair and 15 percent were good. Participants were using interpreters and colleagues to overcome their language barriers while caring for Arabic patients. 6 percent were attending Arabic classes to improve language barrier. 2 participants highlighted the use of non-verbal communication and 1 shared the use of internet sites/ google for translation. 10 percent were using booklets prepared by units for translation of common used terminologies.

**Table 3.** Comfortability while Dealing with Arabic Patients

	FREQUENCY	PERCENT	VALID PERCENT	CUMULATIVE PERCENT
Excellent	6	4.2	4.2	4.2
Good	55	38.2	38.2	42.4
Fair	83	57.6	57.6	100.0
Total	144	100.0	100.0	

### Input Regarding the Communication Tool Kit

In pre-study questionnaire, 94 percent viewed that this communication tool kit will benefit them to overcome their language barrier. 61 percent participants responded that will help them moderately to overcome their language barrier.

### Average Hours given to Use this Tool Kit

As shown in Table 1.4, 38 percent of the participants use this tool kit twice per week and 7 percent never use this tool kit. 22 percent of the nurses use this tool kit on daily basis or as needed.

**Table 4.** Hours Given to this Tool kit

NUMBER OF HOURS	PERCENT
Once Per Week	17
Daily	19
Twice Per Week	38
Once Per Month	16
Never	7
As Needed	3
Total	100.0

### Efficacy and Applicability of the Communication Tool Kit

According to post questionnaire analysis, 83 percent voiced this tool kit as moderated as compared to 13 percent who highlighted this as excellent source of communication (see table 5).

**Table 5.** Efficacy and Applicability of this Communication Tool kit

EFFICACY	PERCENT
Excellent	12.6
Little	61
Fair	22
Poor	2
Total	100.0

### Support required and Suggestions to overcome this language barrier

55 of the nurses responded to this question. Majority 50 percent of the nurses highlighted the demand for Arabic classes. 2 percent demanded for electronic gadget accessibility to patient. 16.3 voiced the need for interpreters. 11 percent identified the need for more communication tool kit accessibility in the unit. 4 percent highlighted the need for appreciation.

**CONCLUSION:** This study has provided information about the need to identify the strategies to overcome the language barrier. In addition, it identifies the nurses' level of comfort while speaking Arabic while caring for Arabic patients. Moreover, it highlighted the efficacy and feasibility of this communication tool kit while caring with Arabic patients.

### Recommendations

In view of study findings, following recommendation may help in bringing about the improvement in the system. The recommendations include:

1. Proper advertisement and flexible time schedule should be made for Arabic classes.
2. Unit specific communication tool kit with pictures should be made.
3. Practice and commitment is required from the nurses to improve their communication.
4. Tool kit should be made on the basis of their language fluency such as basic for beginners, advance for higher level which include sentences.

5. Instead tool kit, flip chart should be accessible to patient's room that includes pictures, words in Arabic and English language.
6. Communication tool kit should be handy or portable that can fix in pockets.
7. Online translation tool or laptop should be available for patient in each room.

### Limitations

This Communication tool kit was beneficial for chronic patients with improve level of consciousness. As most of the time patients were sedated, it was not helpful too much extent. But pictures and word written in English Roman language help the nurses to communicate with sedated patients. Sometimes, it was helpful to speak with patient families as well.

**PROJECT TITLE:** Assessment of Nurses' Knowledge About Autism in Children. RAC #2131 081.

**INVESTIGATORS:** Sana Ghulman, RN, BSN, Masters Candidate

**PROJECT DESCRIPTION:** Poor knowledge and awareness about childhood autism is a major barrier to improving the health and wellbeing of children affected by autism and limits access to care and early interventions that are known to improve quality of life and prognosis in children with autism [18]. Caring for children with childhood autism and other pervasive developmental disorders requires the services of professionals like psychiatrists, pediatricians, nurses, clinical psychologists [19]. So pediatric and psychiatric nurses are a corner stone of multidisciplinary teams. This study will assess knowledge of nurses about childhood autism and identify factors that could be influencing the autism knowledge among pediatric nurses in KFSH & RC at Riyadh in Saudi Arabia. A qualitative explanatory research approach selected for this study and will be applied through non experimental (does not involve a manipulation of the situation, circumstances or experience of the participants), descriptive (description is about fact gathering or what), correlational design (Where two events or

characteristics are correlated we can predict one from the other).

**PROGRESS AND MAJOR FINDINGS:** There was significant differences between the nurses from different specializations and there was also significant differences with nurses who have previous involvement in managing children with childhood autism comparing to nurses who handled them very seldom, regarding the factors affecting the nurses knowledge the most common factor is the gender , female show larger mean than male in all domains.

**CONCLUSION:** The scores reflect deficits in knowledge about childhood autism among the study. Pediatric nurses as members of multidisciplinary teams that care for children with childhood autism are expected to provide holistic care and adequate counselling to the families of these children. Unfortunately, they are not fully equipped with enough knowledge about childhood autism. Education on childhood autism is therefore needed and can be provided through continuing medical education and emphasizing childhood autism in their training curriculum. This will enhance early identification and diagnosis of childhood autism with early interventions that are known to improve prognosis.

**PROJECT TITLE:** The impact of Residency Programs on Saudi New Graduate Nurses' Clinical Decision-Making and Clinical Leadership Skills. RAC #2131 131.

**INVESTIGATORS:** Reem Al-Dossary, RN, BSN, MSc, PhD candidate.

**PROJECT DESCRIPTION:** The purpose of this study is to explore the impact of residency programs on new Saudi graduate nurses' clinical decision-making and leadership skills at baseline entry into residency program and three months of enrolling in the program.

**PROGRESS AND MAJOR FINDINGS:** A convenience sample of n = 98 new graduate nurses was collected from

three hospitals in Saudi Arabia. A self-administered questionnaire was used to collect data. Clinical decision-making skills were measured using Clinical Decision Making in Nursing Scale and clinical leadership skills were measured using the Clinical Leadership Survey. An independent t-test, bivariate association, and multiple linear regression analysis were utilized to test hypotheses concerning different groups.

The findings revealed a significant difference between the residency program group and the nonresidency program group in clinical decision-making ( $t = 23.25, p = 0.000$ ) and leadership skills ( $t = 10.48, p = 0.000$ ). However, there were no significant differences in the average number of clinical decision-making and leadership skills based on the length of their residency program (6 months vs. 12 months). In addition, a moderate positive correlation was found between overall grade point average (GPA) and total clinical decision-making scores ( $r = 0.365, p = 0.000$ ), and overall GPA and total clinical leadership skills ( $r = 0.440, p = 0.000$ ). The clinical decision-making regression model explained 86.9% of the variance in total clinical decision making by the differences in age, overall GPA, and enrollment in a residency program. In addition, the clinical leadership skills regression model explained 60.6% of variance in total clinical leadership skills by the differences in age, overall GPA, total clinical decision-making scores, and enrollment in a residency program.

This study is one of the first such studies that examined the impact of residency programs on clinical decision-making and leadership skills' of new Saudi graduate nurses who completed a residency program. The findings of this study indicate that there is a need to implement more residency programs in hospitals of Saudi Arabia. It is imperative that nurse managers and policy makers in Saudi Arabia consider these findings to improve nurses' clinical decision-making and leadership skills, which will in turn improve patient care.

**PROJECT TITLE:** Nurse's Perceptions of Rapid Response Team in a Tertiary Hospital in Saudi Arabia. RAC #2131 140

**INVESTIGATORS:** Emad Mraweh Mustafa, RN, BSN, Masters Candidate

**PROJECT DESCRIPTION:** Primary care nurses must have the skills and abilities to identify the early signs of clinical deterioration in order to activate the Rapid Response Team (RRT) (Pantazopoulos et al., 2012) and avoid a delay in care. The RRT is not intended to replace the role of the primary team; they are there to work as an adjunct to the primary team and ultimately to decrease the mortality rate (Howell et al., 2012). The nurse's perception of the RRT is considerably important, since nurses must be satisfied with the service provided in order to utilize it in a proper manner (Metcalfe et al., 2008). The purposes of the proposed study is to: 1) explore the relationship between the frequency of activating RRT by nurses and support received from RRT, 2) to investigate nurses perceptions of learning outcomes as result of a number of exposure to RRT cases, 3) identify the factors that affect nurses perception about RRT, 4) and identify the overall impressions of nurses about advantages and disadvantages of RRT. It is expected that nurses who use the RRT more frequently will perceive more support (Knowledge and skills), as well as more positive learning outcomes. The impact of proper utilization of RRT by nurses on the organizational level is expected also; to decrease mortality and morbidity rate, decrease the number of codes, and the unplanned admissions to ICU. A 46 item instrument likert scale will be used for data collection.

**PROGRESS AND MAJOR FINDINGS:** This study had utilized a cross-sectional descriptive correlational design to assess the level of nurses' perception of RRT at individual level, group level, and hospital level, and to assess the overall impression about RRT. All nurses who had worked in the inpatient units which are covered by RRT service were included in the

study sample. 36.6% of the sample had completed the questionnaires. Most participants were females (88.7%), had a mean age average (35.75) years and nurses who had bachelor degree in nursing were (77.3%). The mean average for nurses had worked in the nursing profession was (11.8) years. The internal consistency of the all scales and subscales tool was ranged from 0.887 to Research question one addressed nurses' overall perceptions about RRT service. Four Likert scale questions were asked to measure the overall impression. (See table 3). The four-instrument item instruments indicated that nurses who are utilizing RRT have a high overall impression of RRT. The highest rated item Improving early recognition of patient deterioration (Mean = 5.66) and the lowest mean (Mean = 5.41) was for Gaining knowledge in managing patient deterioration.

There is a relationship between frequency of the RRT utilization and content support ( $r = .131$ ,  $p < .023$ ). However, there is a positive, but non-significant relationship, between frequency of RRT utilization and process support ( $r = .092$ ). Only four respondents out of 300 never called the RRT, 14 individuals made 1 call, 25 people made 2 calls, 25 people made 3 calls, 10 people made 4 calls and most respondents ( $n = 222$ ) made 5 or more calls.

The correlation coefficient test examined the relationships between nurses' perceptions of content and process support provided by the RRT and mental model building and mental model maintenance for self, group and organization. The research question related to self (individual) was moderately supported. That is, significant positive relationships between content support and mental model maintenance ( $r = .665$ ,  $p < .01$ ) and mental model building ( $r = .717$ ,  $p < .01$ ) was found. Similarly, significant positive relationships between process support and mental model maintenance ( $r = .733$ ,  $p < .01$ ) and mental model building ( $r = .74$ ,  $p < .01$ ) were found. It appears that RRTs influenced maintenance and building of mental

models of individuals who were exposed to their services. The part of the research question related to groups was moderately supported. There was a significant positive relationship between content support and mental model maintenance ( $r = .73$ ,  $p < .01$ ) and mental model building ( $r = .717$ ,  $p < .01$ ). Strongly support and significant positive relationships were also found between process support and mental model maintenance ( $r = .767$ ,  $p < .01$ ) and moderately supported and significant positive were also found between process support and mental model building ( $r = .74$ ,  $p < .01$ ). Participants perceived that RRTs had a positive influence on learning outcomes of their work groups.

The last part of the research question related to organization (hospital) was moderately supported. Significant positive relationships were found between content support and mental model maintenance ( $r = .59$ ,  $p < .01$ ) and mental model building ( $r = .519$ ,  $p < .01$ ).

Furthermore, there was a significant positive relationship between process support and mental model maintenance ( $r = .638$ ,  $p < .01$ ) and mental model building ( $r = .564$ ,  $p < .01$ ) for perceptions about the hospital. Participants appear to see an effect of RRTs on organizational learning.

77 (25.7%) of nurses wrote that the greatest advantage of RRT is improving patients' safety by early detection and intervention for the deteriorating signs. 70 (23.3%) of nurses reported that RRT prevents adverse events and further deterioration, while 65 (21.7%) of nurses found that RRT is a support and help for nurses. There were 25 (8.3%) nurses reported that RRT decreases the chance of code, while only 12 (4%) of nurses reported that RRT improves the team work and nurses knowledge.

The majority of nurses (70%) reported that there are no disadvantages for RRT. 17 (5.6%) nurses found that RRT members need to improve their communication and physical assessment skills, and 10 nurses reported that RRT members delay

transferring sick patients to the ICU due to ICU bed unavailability.

Nine nurses reported that RRT increases the workload for them, while only eight nurses found that RRT members step on nurses' role and responsibilities.

The socio-demographic part of the study provided information about the characteristics of the sample. . The majority of the participants were female nurses (88.7%) which was expected, as most of the nurses who participated in the study that was conducted were female, had an age range from 24 to 62 years with a mean average of (35.75± 8.699) years old. The majority (77.3%) of the participants held a Bachelor degree in nursing as their highest education achieved. This high number of bachelor degree nurses can be explained by the hospital recruitment strategy.

The hospital is highly concerned about recruiting qualified nurses with a high level of education, and encouraging nurses to continue their education by providing a fund support and flexible work scheduling. This support explained having seven nurses from the sample holding master degree.

The mean score for the level of experience was (11.8± 7.915). Only one participant had working experience less than one year, and this explained by the hospital recruitment policy that nurses should have minimum of two years' experience as one of the recruitment conditions. (37.3%) had critical care experience worked in different settings, such as step-down units, intensive care units, and emergency room, in comparison to Johal (2008), who used the same tool, (44.5%) of the participants had critical care experience. The previous sample characteristics used under the factors that positively affect nurses' perception of individual level, group level, and hospital level about RRT, and those factors were critically discussed in the literature review.

This study is considered the first one in the Middle East that had examined the nurses' perception of

the RRT by using mental model maintenance and building. Additional future researches should be conducted to support the findings of this study. Future studies should use a larger sample from different hospitals and centers. Inclusion of multidisciplinary teams who are able to activate the RRT is also recommended. Comparing the relationship between the study variables in more than one hospital would provide a more realistic reflection regarding the relationship between those variables. Inclusion of more variables such as marital status and nationality could provide better correlation between participants' demographics and the study variables. Inclusion of nursing educators, managers, and physicians should be considered in future studies as they may provide valid information, as nurses in the principle investigator's hospital from more than 25 different nationalities. Longitudinal researches would also provide more powerful information about nurses' perception of the RRT. Also the data from this study can be used to design and test a specialized educational program on patient deterioration that includes identification and testing of content and process support. The effect of developing a training program should lead to staff nurses feeling more comfortable with caring for deteriorating patient and become more autonomous in noticing small changes in patients to prevent failure to rescue.

**PROJECT TITLE: Empowering Experience for the Frontline Nursing Managers at Single Tertiary Center at Kingdom of Saudi Arabia. RAC #2141 058**

**INVESTIGATORS: Ammin Abuelshaer, RN, Msc**

**PROJECT DESCRIPTION:**

**Background:** The nursing staff empowerment at work place has been explored and discussed extensively within the literatures; while it's very clear that few researches only have been done to explore the empowerment of the nursing managers and in specific the frontline ones who needs to empower others.

**Aims & Objectives:** The purpose of this study is to assess the frontline nursing manager's perception about the organizational structure at King Faisal Specialist Hospital-Riyadh.

**Method:** A non-experimental quantitative, descriptive cross sectional study will be used to measure organizational empowerment among head nurses, assistant head nurses, nursing supervisors, education coordinators, and clinical coordinators who are performing a managerial job, in a 936-bed hospital accredited by joint commission. A modified Nurse Work Empowerment Scale Questionnaire II (CWEG-II), will be distributed and validated on 25 frontline nursing manager and then will be distributed to 75 nursing manager.

**PROGRESS AND MAJOR FINDINGS:** Currently on data analysis.

**PROJECT TITLE:** Leading a Transient Workforce in a Tertiary Care Hospital. RAC# 2141057.

**INVESTIGATORS:** Ilse Ackermann, RN, BSN

**PROJECT DESCRIPTION:** The aim of this study is to identify factors that impact leadership and change within a transient workforce. The researcher will be adopting a Phenomenology philosophy. It will be a study about how leadership appears to the middle managers and "how people experience the world" (Fisher, 2010, p.62). This is also referred to as social constructionist research or an interpretivism approach. The focus will be on how people provide meaning through interaction (Robson, 2011). To explore the research objectives, an inductive approach will be used. This study will attempt to build on theory and provide a theoretical explanation of the data collected and compare it to published theory (Saunders, 2012).

The researcher will be conducting a qualitative research. Data collection will be conducted through semi-structured interviews amongst middle managers in the identified hospital. Qualitative research is normally non-numerical and use data

collected through words (Robson, 2011). "Qualitative research studies participants' meanings and the relationships between them" (Saunders, 2012, p.163). A flexible design will be incorporated, which implies that although this research "involve preliminary planning; it does not include fixed procedure details in advance" (Robson, 2011, p. 5). This paper proposes to be an exploratory study, because new knowledge might be obtained (Saunders, 2012, p. 171). The researcher intends to keep a reflective diary to record any important events, feelings, dates and anecdotal notes (Fisher, 2010). This study will be a cross-sectional one," as the data will be collected in a single point in time" (Robson, 2011, p.127). One interview will be conducted per participant. This is due to the time constraints of this academic study (Saunders, 2012). The research population of this study are the middle managers of a large tertiary care hospital in the Middle East. Exploratory samples will be used, because it is a small scale study where a qualitative strategy will be implemented. Non-probability sampling or purposive sampling technique will be indicative, as the researcher will select who to interview. The researcher proposes to select a sample size of 8-10 participants and to obtain an even number of out-patient and in-patient Head Nurses. The participants must have at least three years leadership experience in this organisation. This will ensure a robust study, as many leaders are also transient. During this qualitative research study, one-to-one, semi-structured interviews will be conducted. Open ended questions will be asked to obtain as much new information as possible. All interviews will be tape recorded (audio) (Denscombe, 2012). Data collection will be non-standardised to allow for any questions that might arise during the research process. This will provide some flexibility to pursue any further lines of inquiry (Saunders, 2012). The interviews will last approximately one hour. All participants will receive a preparatory brief from the researcher, to explain the extent and goal of this research study. The researcher will be utilizing content analysis to analyse the data, because of its qualitative nature.

Content analysis is utilized to quantify the text part of the data collection (Denscombe, 2012).

**PROGRESS AND MAJOR FINDINGS:** Interviews are being conducted. Content analysis to be finalized by 2015.

**PROJECT TITLE:** Work Experiences of Nurses With Different Cultural Background in Riyadh. RAC#2141077

**INVESTIGATOR:** Angelina Fernandez, RN, BSN, MSN candidate

**PROJECT DESCRIPTION:** The aim of this study is to explore the experiences of nurses at work with multicultural backgrounds. A qualitative exploratory method will be used to conduct this study. Fifteen in-depth interviews will be conducted and inductive content analysis will be applied to draw conclusions.

**PROGRESS AND MAJOR FINDINGS:** Content analysis is currently being conducted.

**PROJECT TITLE:** Cross-Sectional Survey to Determine Perceived Personal and Environmental Barriers to Healthy Eating Among Nurses at King Faisal Specialist Hospital and Research Centre, Riyadh City, Kingdom of Saudi Arabia. RAC #2141139.

**INVESTIGATOR:** Pauline Gambiza RN, BSN

**PROJECT DESCRIPTION:** The purpose of this study is to establish perceived personal and environmental barriers to healthy eating among nurses that work at King Faisal Specialist Hospital and Research Centre (KFSH&RC). Nurses play an integral role in health promotion, helping the communities achieve optimal health through collaborative relationships in the management of their health, which include barriers to healthy eating. For nurses to be effective health promoters it is important to understand the personal and environmental barriers they encounter to adhere to healthy eating to implement necessary interventions to reduce these barriers. A

cross-sectional design will be applied in order to capture a snapshot of the proportion of personal and environmental barriers to healthy eating among the defined population.

**PROGRESS AND MAJOR FINDINGS:** Data being currently collected.

**PROJECT TITLE:** Work Environment Challenges Faced by Malaysian Nurses Working in a Hospital in Saudi Arabia. RAC #21410140.

**INVESTIGATORS:** Yean Ching Chew RN, Chew Yen Yong RN

**PROJECT DESCRIPTION:** Nurses who take expatriate positions are expected to perform consistently well virtually from the very moment they start their appointment in the host country (Bozionelos, 2009). They faced with many challenges in a multicultural environment in relation to language, customs, communication, and healthcare practices (Brady & Arabi, 2005), in addition to adjustment to different climate, new work environment and changes in job responsibility (Hechanova, Beehr, & Christiansen, 2003). There is a scarcity of research focusing on issues encountered by international nurses in their adjustment to foreign health-care environments (Kawi & Xu, 2009), non for Malaysian nurses as yet. As such, it is dynamic for researchers to ascertain what challenges faced by the Malaysian nurses who are coming from a similar Muslim religious country and multicultural background in order to ease and support their integration into new workplace environments. This study will use quantitative approach and non-experimental descriptive cross-section design to identify the significant challenges faced by Malaysian nurses. It is a non-probability, convenience sampling of Malaysian nurses who are currently employed at a hospital in Riyadh, Saudi Arabia. Inclusion Criteria are all registered nurses who are holding a valid Malaysian Nursing Board license to practice at the hospital. Exclusion Criteria are nurses who are non-Malaysian and nurses who refused to participate in the research.

**PROGRESS AND MAJOR FINDINGS:** Initial stage of data collection.

**PROJECT TITLE:** Readiness Evaluation and Discharge Interventions - READI: Implementation as a Standard Nursing Practice For Hospital Discharge: A Multi-Site Nursing Research Study. RAC# 2141 059.

**INVESTIGATORS:** M. Sofia Pires Macedo, RN, BSN, PG, MSc EBHC (c), Abeer Hussain, RN, BSN, Alun Woodhouse, MA, BSc (Hons) RN-BC, Karemah Ahmad Alrabghi, RN, BSN, Lorrie Bushby, RN, Rosevie Segismundo, RN, BSN, Yin Yin Chooi, RN, BSN

**PROJECT DESCRIPTION:** Reducing readmission and Emergency Department (ED) utilization rates is central to health care improvement and reform efforts. With readmission rates approaching 20% and financial penalties for high 30 day readmission rates, novel approaches to engaging hospital nurses in readmission reduction efforts are needed to improve quality and affordable care. Problems with hospital discharge are well documented. Most readmissions within 30 days are viewed as preventable and failures of discharge preparation. Discharge preparation is a primary function of hospital nurses (RNs). Readiness for discharge is an outcome metric of the hospitalization phase of care and has a risk indicator for readmission. Yet discharge readiness assessment is not a standard of nursing practice for hospital discharge.

**Purpose of the study:** The aim of the study is to evaluate the impact on outcomes and costs of implementing discharge readiness assessment as a standard practice on nursing units. We will sequentially evaluate 3 implementation protocols to determine the best approach for achieving improvements in readmission and ED use post-discharge.

Using a prospective, parallel cohort, stepped intervention study design, we will implement, in sequence, 3 discharge readiness assessment protocols and compare readmission/ED use results to a paired control unit.

**Protocol 1:** 8- item Readiness for Hospital Discharge Scale – RN form (RN-RHDS) administered on the day of Discharge by the discharging nurse. **Protocol 2:** Protocol 1 with the addition of 8 item PT-RHDS completed by the patient and reviewed by the discharging nurse. **Protocol 3:** Protocol 2 with the addition of a Nurse Initiated Action Form (NIAF) to document actions taken in response to discharge readiness assessment. Action required for RHDS scores <7. Hospitals will identify 2 units of the same type (medical, surgical, or medical-surgical). The implementation and control units will be randomly selected. Patients: Adult medical surgical patients who are discharged home without hospice care. Sample will include all eligible patients. Nurses: All RNs on implementation units.

**Data collection:** Implementation Units: Discharge readiness assessment using RHDS will be conducted by the discharging nurse on the day of discharge. Patient characteristics and readmission/ED use will be extracted from electronic records. Control units: There are no on-unit data collections. Patient characteristics and readmission/ED use will be extracted from electronic records.

**Study Team Role and Visibility:** The study team will work with site coordinators at each site to plan for study implementation including IRB approval, data collection logistics, staff training, and electronic data acquisition. A research team member will be assigned as a direct liaison and will be on site during study start-up. Communication throughout the study will occur via video-assisted web conferencing. Site specific and total study results will be provided to each site.

**PROGRESS AND MAJOR FINDINGS:** Data collection to be initiated in May 2015.

#### **NURSING RESEARCH AND EVIDENCE BASED PRACTICE PUBLICATIONS:**

- Abudari G., Zahreddine H., Hazeim H., Al Assi M., Emara S. "Knowledge of and attitudes

- towards palliative care among multinational nurses in Saudi Arabia" *International Journal of Palliative Nursing*. 2014, Vol 20, No 9.
- Aboshaiqah , A. E., Hamdan-Mansour A., Sherrod D.R., Alkhaibary A., Alkhaibary S., "Nurses' Perception of Managers' Leadership Styles and Its Associated Outcomes." *American Journal of Nursing Research*, vol. 2, no. 4 (2014): 57-62. doi: 10.12691/ajnr-2-4-1.
  - Macedo MS (2014) Use of systemic antibiotics and antiseptics for venous leg ulcers. *Nursing Times*; 110: 25, 16-17.
  - Macedo M.S. (2014) Non-pharmacological interventions for fatigue in rheumatoid arthritis. *Singapore Nursing Journal*. 41(2) April – June: 48-50.
  - Macedo MS (2014) Dietary Supplements for Preventing Postnatal Depression. *Clinical Nurse Specialist*. Nov.-Dec. 318-319.





