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King Faisal Specialist Hospital & Research Centre
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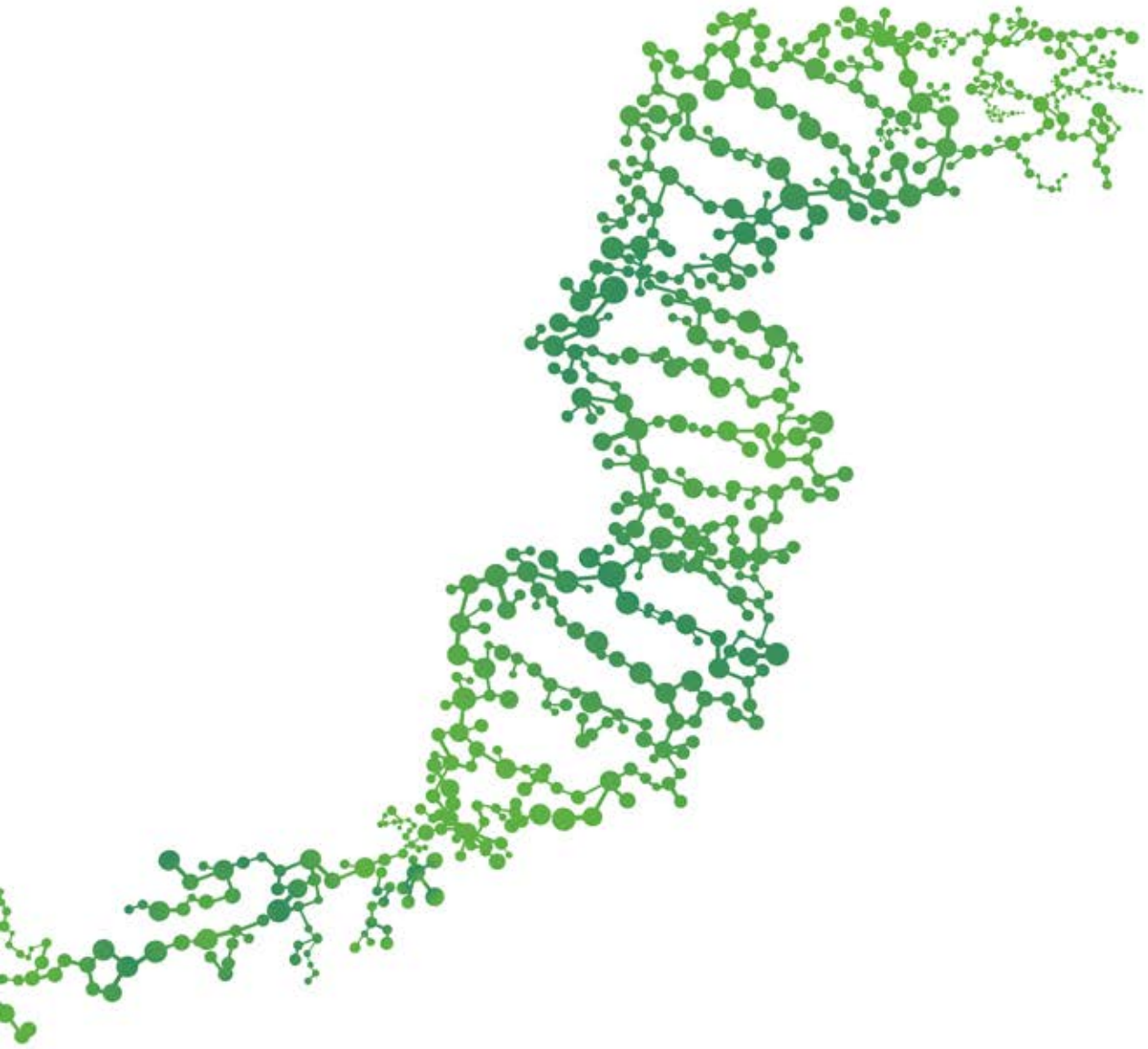

2011 RESEARCH REPORT

2011 RESEARCH REPORT

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.

A message from the Chief Executive Officer

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

IT IS A PLEASURE TO SHARE WITH YOU OUR ACCOMPLISHMENTS IN 2011. at KFSH&RC, we take pride in the enthusiasm of our scientists, physicians and researchers who work collaboratively to address critically challenging issues in healthcare. The pages that follow will demonstrate how joint commitments of time, energy and perseverance can lead to promising research results.

Research activities continue to play a vital role at KFSH&RC in its mission to deliver the highest standard healthcare in Saudi Arabia. This role continues to expand as healthcare demands increase and as patients' concerns become more sophisticated. The 2011 Annual Research Report showcases the variety of innovative methods utilized by our doctors, scientists, and researchers to deliver exceptional translational research results which lead to better classification, diagnosis, management and treatment of disease.

This past year we have seen the successful restructuring of the Research Centre in order to support and facilitate new developments through the creation of new entities such as the Molecular Biomedicine Program, The National Biotechnology Centre, and the Molecular Oncology Department.

Additionally, KFSH&RC has been designated as the Kingdom of Saudi Arabia's representative in the international Cancer Genome Consortium, which is comprised of world leading institutions working together to build the most comprehensive catalog of more than 25,000 tumors.

The Biotechnology Fund continues to provide substantial support to our research endeavors. There are currently seventy-seven (77) million Saudi Riyals committed to forty (40) research projects with an additional eighteen (18) million Saudi Riyals expected for nine (9) approved research projects. In closing, I applaud the hard work and dedication of each and everyone involved in the success of the 2011 Annual Research Report.

A message from the Executive Director

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

SINCE THE INCEPTION MORE THAN THREE DECADES AGO, THE RESEARCH Centre has not stopped looking for ways to maximize its impact and influence in the provision of quality healthcare to the people of Saudi Arabia. From its modest mandate of manufacturing radiotracers for the diagnosis and treatment of cancer patients, The Research Centre's reach has expanded to include promising work in the areas of cancer, cardiovascular diseases, genetics, environmental health, and infectious diseases among others.

Today, its programs in molecular biology, stem cell research, genomics, bioinformatics, and biotechnology generate palpable excitement and interest from many research communities around the world, spurring long-term collaborations and mutual beneficial partnerships.

This annual report chronicles our commitment to excellence and our pursuit of a greater impact in the healthcare landscape in the region. As we witnessed the close of 2011, we are encouraged to see the stronger link between research and clinical practice at KFSH&RC as can be seen in the increasing number of improvements in the diagnosis and treatment of disease. While this is very encouraging, we have to be vigilant as dramatic advances in research have also triggered an explosion of data that, if not used properly, can confound and potentially endanger many established partnerships today. It is therefore important to ensure the correct and proper interpretation of research results at all times. In addition, the relationship between our researchers and our clinicians must be protected to avoid any disconnect between scientific advances in research and the translation of these advances in the clinic. Without this symbiosis, no amount of excellent research work can take us closer to achieving our mission.

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RESEARCH CENTRE

BIOSTATISTICS, EPIDEMIOLOGY AND SCIENTIFIC COMPUTING

Biostatistics Section

ACTING HEAD
Dilek Colak, PhD

MEMBERS
Mohamed Shoukri, PhD
Abdelmuniem Eldali, MSc
Salah I. Al Gain, MSc
Samia Al-Hashim, BSc
Abeer Turki Al-Firm, BA

The mission of the Biostatistics Research Unit (BRU) is to serve as a source of expertise and a focus for research, services and training in the quantitative aspects of health and to provide outstanding statistical support to clinical, applied, translational, and biomedical researchers while advancing the reputation, research capacity, and commitment of the King Faisal Specialist Hospital and Research Centre to advance the understanding, diagnosis, treatment, cure and prevention of human diseases.

The BRU is actively involved in numerous projects, including projects funded by KACST, KSU-KACST, or PSCDR, and collaborating extensively with scientists from various departments of the Research Centre, clinicians at the hospital, as well as other individuals within the Kingdom and abroad. The research projects are related to development and application of statistical and computational techniques to better understand human diseases and the mechanisms underlying them, including several complex diseases, such as cancer, autism, unknown chromosomal disorders, cardiovascular disease, metabolic and developmental diseases and others.

The BRU has an extensive list of publications in reputable peer-reviewed international journals covering the field of biostatistics, oncology, genetics, neurology, public health, ophthalmology, cardiology, endocrinology, and others, resulting from independent biostatistical research as well as collaborative research with other departments at the KFSH&RC, and with regional and international institutions. In year 2011, the Section has published 23 peer-reviewed journal articles, 1 book chapter, and three abstracts. Two of these publications have been awarded KFSH&RC's "*Best Publication Award for Year 2011*".

RESEARCH PROJECTS

PROJECT TITLE: **The Saudi-Arab diseasome - a network of diseases: A comprehensive integrated network-based analysis using genomic, transcriptomic and proteomic data sets for identification of potential markers for diagnosis, prognosis, and therapeutic outcome for Saudi diseases**

RAC # 2110 006 (KACST/NCPST funding # 11-BIO2072-20)

INVESTIGATORS: *D Colak (PI), N Kaya, C Adra, AA Alaiya, M Dagestani, SM Amer, B Karakas*

PROJECT DESCRIPTION: The project led by Dilek Colak, Ph.D. in collaboration with investigators from Molecular Oncology, Genetics, Stem Cell Therapy Program, Infection and Immunity, as well as international collaborators from Dana Farber Cancer Institute, Harvard School of Public Health, and Wayne State University started an initiative to create and explore the first systems of Saudi disease network by using the genome-wide molecular measurements integrated with the human interactome data. The project has currently been approved for KACST/NCPST funding for two years.

A disease phenotype generally reflects various pathobiological processes that interact in a complex network. The highly interconnected nature of the human protein interaction network (interactome) indicates that, at the molecular level, it is difficult to consider diseases as being independent of one another. Contemporary approaches for the classification of human diseases are based on the observational correlation between clinical syndromes and patological analysis. However, this classification suffers from a lack of sensitivity to detect diseases before the presentation of symptoms and in some cases ambiguity in disease diagnosis. Genome-wide molecular measurements, data mining, and bioinformatics approaches have provided the means to explore human diseases from a molecular basis. The exploration of diseases and a system of desease relationships based on integration of genome-wide molecular data with the human interactome could offer a powerful perspective for understanding the molecular architecture of diseases.

In this project, we will identify subnetwork markers for diseases in the Saudi/Arab population using integrated network-based approaches. We will use biomolecular data sets (genome-wide gene expression profiles, Single Nucleotide Polymoprhisms (SNPs) and Copy Number Variations (CNVs), proteomics based protein profiles) that the collaborators of this project previously studied in other approved projects as well as other publicly available datasets at the genomic databases for diseases such as several types cancers (breast cancer, liver cancer), neurological disorders, metabolic disorders, cardiovascular diseases and others. Our results will elucidate the relationships among those diseases at the molecular level. We will create the first Saudi/Arab "Diseasome", a network of diseases; hence to identify how closely all disease disorders similar/distinct from each other and elucidate common molecular origin of several disorders.

PROGRESS: A manuscript is published in AGE (DOI 10.1007/s11357–012–9404–z) 2012 Apr 4. One book chapter was published. A patent is to be registered. Further data collection and method development analyses underway.

PROJECT TITLE: **Genomics, Transcriptomics, and Proteomics Analysis of Ovarian Hyperstimulation Syndrome: A comprehensive molecular look to a complex syndrome. (Grant from KSU-KACST Joint Grants Support for Center of Excellence)**

RAC # 2100 002

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

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

regions and factors that can be further evaluated as likely biomarkers for the treatment of this disease.

PROGRESS: This project has been approved by KSU-KACST Joint Grants Support for Center of Excellence, and RAC. We have collected more than 160 samples (Polycstic Ovarian Syndrome) and performed Axiom™ myDesign™ GW genechip arrays, cytogenetics whole-genome 2.7 M arrays, human genome U133 plus 2.0 array (all from Affymetrix Inc.) on selected patient samples. Our preliminary experiments, data analyses and results indicate possible role of likely molecular factors involving in molecular mechanisms of OHSS. The study is still in ongoing phase and further sample collection with OHSS and additional experiments are to be performed.

PROJECT TITLE: **Likelihood inference on the relative risk in split-cluster designs**

RAC # 2090 030

INVESTIGATORS: *M. M. Shoukri and D. Colak*

PROJECT DESCRIPTION: Split-cluster experiments are widely used by investigators in health sciences when naturally occurring aggregate of individuals with nested subgroups may be assigned to different interventions. Cited examples include the split mouth trials, in which a subject's mouth is divided into two segments that are randomly assigned to different treatment groups. When the response variable of interest is binary, statistical methods developed to evaluate the effect of interventions depended on non-parametric methods. These methods are simple to apply, but are known to be less efficient. In this paper we establish a full likelihood inference procedure and develop a score test on the significance of the relative risk as a population effect size.

Cluster randomized (CRT) trials in which intact social units of subjects are randomized to receive either a treatment or control intervention are ubiquitous in health research. Examples are school- based smoking cessations trials with subjects clustered within work sites (Hedeker et al 1994) or schools (Gail et al 1992, Peterson et al 2000). Trials randomizing smaller clusters such as families (e. g. Farr et al 1988) have also been reported.

Given its statistical inefficiency, reasons for adopting this design tend to rest on logistic, financial and/or ethical considerations. In the "completely randomized" design k clusters are randomly assigned to each of two interventions. In the frequently adopted matched pair design (MPD), subjects within each of the k matched pairs of cluster are randomized to receive one of two interventions, where common matching characteristics include cluster size and baseline versions of the outcome variable. A special case of this design arises when the cluster is split into two sub-clusters, and subjects within each sub-cluster receive one of the two interventions (the "split-cluster" design). A frequently occurring example is the "split-mouth" design adopted by periodontal researchers, in which the mouth is divided into two experimental sections that are randomly assigned to one of the treatment groups. Similar examples in the field of dermatology are given in Bigby and Godenne (1986).

In this project we construct a bivariate correlated model that allows us to estimate and test hypotheses concerning the interclass correlation coefficient P_{12} in a MPD with binary outcome data. Since the efficiency of this design increases with the magnitude of P_{12}, such a test may be useful in establishing its overall efficiency as compared to the completely randomized design.

This project has three specific objectives: Taking the relative risk R as an effect measure we first use moment estimators for this parameter to construct Wald and Feiller-based confidence intervals. However these methods are not likelihood-based and are known to be less efficient than those based on full likelihood based inference. Therefore we also construct a bivariate correlated model under which a score test is applied to test Ho:R=1.0. Finally, we present a goodness of fit procedure for testing Ho: $P_{12}= 0$.

PROGRESS: A paper has been published in Clinical Trials, Feb. 2011 8: 37–47.

PROJECT TITLE: **Establishing Equivalence of Two Treatments using Neyman's C(α) Test**

RAC # 2050 002

INVESTIGATORS: *M. M. Shoukri and D. Colak*

PROJECT DESCRIPTION: The determination of BE is very important in the pharmaceutical industry because regulatory agencies allow a generic drug to be marketed if its manufacturer can demonstrate that the generic drug is bio-equivalent to the brand-name product.

The statistical methodologies to establish equivalence have relied on modifications of both confidence intervals construction and the Two-one-sided test of Schuirmann 1987. In such studies the issue is philosophically different from the classical statistical testing the equality of two population means. In a typical BE study we need to demonstrate that the two active drugs are equivalent within a priori stipulated acceptance limits. That is equivalence is the alternative hypothesis and non-equivalence is the null hypothesis.

There are two competing designs under which BE can be investigated; the first being the parallel-groups design and the other is the crossover design. For both designs, the methodologies for establishing equivalence have focused on the application of Feiller's theorem (1954) for the normal data and the likelihood ratio test for categorical data. In this project we shall use an entirely different technique for inference. The theoretical underpinning of this approach was developed by Neyman (1937) and later extended by Moran (1973). The approach was termed by them "the C(α)" testing procedure. It possesses an interesting property in that it is locally most powerful against alternatives in the neighborhood of the null.

PROGRESS: The C(α) test for the multivariate normal response was derived, and initial results for the binary response case are obtained. It turns out that the derived model for the binary response case is a member of the bivariate beta binomial family of distributions. We have developed several competing test statistics to compare their performance in terms of power and empirical levels of significance to the Neyman's C(α) test. Monte Carlo simulations have been conducted to achieve this objective. A final report has been submitted to ORA. A manuscript is under preparation.

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

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

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

PROGRESS: This project has been approved by KACST Biotechnology grant program. Data collection and initial analyses have been performed. A manuscript is under preparation.

PROJECT TITLE: **Identification of Environmental and Genetic Factors that Influence Breast cancer development and therapy in Saudi females**

RAC # 2031 091

INVESTIGATORS: *Suad M Bin Amer, D Colak, M Nirmal, H Jeprel, A Nofal, T Tweigeri, A Tulbah, D Ajarim, O Al Malik*

PROJECT DESCRIPTION: Breast Cancer is the major cause of morbidity and mortality among females

in Saudi Arabia. Clinical observations indicate that the breast cancer developed before the age 45 accounts for 45% of all female breast cancers in Saudi Arabia as compared with only 9.6% in USA. Breast cancer in young Saudi females is more aggressive in nature with poor prognosis and disease free survival. Thus new diagnostics, prognostic and therapeutic markers are needed. We conducted a comprehensive analysis of global gene expression changes to characterize the underlying biological mechanisms of young age breast cancer in Saudi Arabia. We also investigated gene expression profiles of cancer progression from normal to preinvasive stage of ductal carcinoma *in situ* (DCIS) and to potentially lethal stage of invasive ductal carcinoma (IDC).

PROGRESS: We analyzed the whole-genome mRNA expression profile from tumor and adjacent disease free tissues of 115 samples using Affymetrix GeneChip Human Genome U133 Plus 2.0 Arrays. Both unsupervised and supervised analyses were performed. We have identified 77 signature genes specific to tumor in young age (≤ 45). Array findings were validated using real-time RT-PCR, immunohistochemistry, and *in silico* validation analyses. Functional and pathway analysis revealed some distinct and shared functional categories and pathways among three age subgroups. Moreover, we studied molecular alterations associated with cancer progression in young women using cross-species comparative genomics approach. Breast cancer appearing in young women represents distinct biological characteristics with unique deregulated signaling pathways. We presented our results at local and international conferences. One manuscript is submitted for publication.

PROJECT TITLE: **Molecular genetic studies in chromosome disorders**

RAC # 2040 042

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

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

PROGRESS: We have collected samples from patients (mainly children) based on our inclusion criteria. We performed high-resolution aCGH using Agilent high-density chips, linkage, CNV, and genome-wide gene expression studies using Affymetrix GeneChip SNP and gene expression assays. We performed the data analysis and obtained initial results. We are also in the process of targeting and sequencing the candidate genes from the genome-wide scan analysis, and identify genes or groups of genes underlying the dysmorphic syndromes. Three manuscripts are published in 2011.

PROJECT TITLE: **Molecular Characterization of Autism Spectrum Diseases: A Pilot Study for Three Distinct Disorders**

RAC # 2040 024

INVESTIGATORS: *Kaya N, Colak D, Al-Odaib A, Demirkaya O, Sakati N*

PROJECT DESCRIPTION: This is a pilot study to test the hypothesis that the individual disorders existing in the autism spectrum might share disturbed molecular and physiological pathways. For this purpose four disorders within the autism spectrum diseases phenotypically different but all of which manifest autism have been selected: Fragile-X with autism, Rett syndrome, osteopetrosis with autism, and very early and severe infantile autism. The aforementioned hypothesis will try to determine the gene signatures related to autistic derangements within each autistic disorder by detecting changes in genetic pathways by comparing our findings from autistic patients to appropriate normal matching siblings. Moreover, the alterations established in these disorders will be further compared among groups to whether common denominator(s) can be detected. This approach will help to establish a link between genetic alterations and gene signatures within and among the diseases of interest.

PROGRESS: We have performed gene expression profiling using Affymetrix's Human HG-U133 Plus 2.0 gene expression chips on whole blood RNA from patients and sex and age matching controls. We have identified significantly altered genes that are common among the autism spectrum diseases. Functional and pathway analysis have been performed. Two manuscripts are published in 2011.

PROJECT TITLE: **Pathogenesis of Early Infantile Primary Lactic Acidosis**

RAC # 2050 009

INVESTIGATORS: *Al-Owain M, Kaya N, Colak D, Al-Odaib A, Tbakhi A, Al-Hasnan Z*

PROJECT DESCRIPTION: This study aims to establish the sequence of pathological events in early infantile lactic acidosis patients. This will be achieved by serially studying the apoptosis and the derangement of the nuclear/mitochondrial oxidative phosphorylation (OXPHOS) genes and their transcription profiling in such infants. The gene signatures in whole blood and identification of key genes likely to participate in the apoptotic and nuclear / mitochondrial dialogue for this disease will be performed using ABI 1700 Microarray system. Linkage experiments as well as fine mapping experiments will also be performed on familial cases.

PROGRESS: We have collected blood from nine patients from different parts of Saudi Arabia. Global gene expression profiling was performed on patients and age and sex matching controls using ABI 1700 system. The differentially expressed genes in patients compared to controls have been determined The unsupervised clustering analysis clearly separated individuals based on their subject group. Functional annotation and biological term enrichment analysis were performed. Also, Linkage analysis on familial cases and fine mapping and sequencing of targeted genes have been performed. A manuscript is under preparation.

PROJECT TITLE: **Gene expression and immunohistological finding in patients with Papillion Lefevre Syndrome**

RAC # 2070 022

INVESTIGATORS: *A Alomrani, N Kaya, D Colak, S Al-Muhsen, M Al-Owain, H Al-Zaidan, C Ullbro, R Hakansson, S Dermime*

PROJECT DESCRIPTION: Papillon-lefevre syndrome is an autosomal recessive disorder characterized by hyperkeratosis of palm and soles and by a generalized aggressive periodontitis and premature loss of primary and permanent dentition. It is relatively prevalent in a small village north of Riyadh with more than 60 patients being followed in the dental clinic at KFSH&RC. Severe periodontal disease plays an important role in PLS resulting in premature loss of primary and permanent dentition. Two mutations have been identified in the cathepsin C (CTSC) gene in this population. The aim is to study the histopathology, immunological profile, and gene expression of PLS from blood samples and gingival biopsies; and thus shed more light on the pathophysiology of the disease and explore whether new subclasses of this disease can be identified based on gene expression profiles. Furthermore, we aim to establish a preventative program among this high-risk group through carrier testing and genetic counseling.

PROGRESS: Mutation analysis has been performed on the collected samples. We are in the process of collecting more samples.

PROJECT TITLE: **Proteomic analysis of human breast cancer stem cells/progenitor cells**

RAC # 2080 021

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

PROJECT DESCRIPTION: In mouse models, it has been proven that breast cancer stem cells exclusively retain the ability to form new tumors and they display stem/progenitor cell properties. They have been

recently isolated and propagated *in vitro*, and recognized as CD44+CD24- breast tumor cells. The goal of this study is to investigate the critical molecular alterations affecting breast cancer stem cells, and how they interact with their microenvironment and the phenotypic characteristics of mammary stem cells will be defined at the protein level, using proteomics approach.

PROGRESS: We have used stem cell markers to isolate cancer stem cells and subjected to proteome analysis by 2–DE. Global protein fingerprints were generated from sorted normal progenitor/stem cells adjacent to tumor as well as normal breast tissues from healthy individual. The results are presented at an International conference.

PROJECT TITLE: **Positional Cloning of genes underlying genetics disorders with prominent neuro-developmental manifestations in several extended families**

RAC # 2060 035

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

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

PROGRESS: DNA samples have been collected from consanguineous familes. SNP-based genotyping, linkage analysis, homozygosity mapping and mutation analysis were performed. A novel mutation is found. Three manuscripts are published from this project in 2011.

PROJECT TITLE: **Role of RORγt Transcription Factor in the Immune System Development, Autoimmunity and Transformation**

RAC # 2080 046

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

PROJECT DESCRIPTION: RORγt, a member of the hormone nuclear receptor super family, is a transcription factor that activates or suppresses many genes. The function of RORγt was studied in multiple mouse models that are deficient in RORγt. RORγ-/- mice lacks both RORγ and RORγt (an isoform variant of RORγ) and RORγtGFP/GFP mice that do not express RORγt but express EGFP instead. These mouse models showed that RORγt expression is restricted exclusively to a limited number of cell types in the immune system, specifically: double positive (DP) thymocytes, lymphoid tissue inducer (LTi), crypto patches (CP), isolated lymphoid follicles (ILF), and T helper -17 (Th17) cells. RORγt was shown to be indispensible for the development of secondary immune organs such as Peyers patches (Pp), and lymph nodes (LN). Other defects due to RORγt loss are also observed: proliferation/apoptotic defects in DP thymocytes, inefficient DP thymocytes development, lack of CP and ILF, enlarged spleen and absence of Th17 cells. Moreover, RORγt is implicated in the development of autoimmune diseases and thymic lymphoma.

Our knowledge of the molecular mechanisms by which RORγt controls the development of immune cells, organs and structures and protect against autoimmunity and thymic lymphoma is lacking. This proposal is a step towards a better understanding of these mechanisms. We think that in order to understand these processes, we need to understand: first, what controls RORγt expression and why it is restricted to only small numbers of immune cell types; second, the genes that are regulated by RORγt; and third, what proteins interact with RORγt to facilitate its function. This understanding will help us understand, not only the development of DP thymocytes, LN, Pp, CP, ILF, and Th17, but also the process by which RORγt protects us against autoimmune and lymphoma diseases. On the long run, this information will help in the diagnosis, drug design and treatment of such diseases in human in a similar fashion to the success story with estrogen receptor and breast cancer.

PROGRESS: Funding received from KACST. The experiments are still ongoing.

PROJECT TITLE: **Micro RNAs as biomarkers for diagnosing breast cancers**

RAC # 2110 016

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

PROJECT TITLE: **Determination of the Cutoff Value of Cytomegalovirus (CMV) Viral Load that is Indicative of Infection in Hematopoetic Stem Cell Transplant Patients**

RAC # 2081 085

INVESTIGATORS: *Jameela Edathodu, MD (PI), Abdelmoneim Eldali, MSc (BRU I)*

PROJECT DESCRIPTION: Breast cancer remains one of the most common cancers affecting women worldwide. To date, several genetic, epigenetic (e.g. DNA methylation), as well as proteinaeous 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 need to identify robust, specific as well as sensitive biomarkers that will be useful for detecting breast cancers and differentiate between agressive *vs*. non-agressive tumors. Micro-RNAs (niRs) are small 18–24 nucleotide RNAs which regulate the expression of approximately 30% of human genes and whose expression is frequently dysregulated in cancers. Contributions from a number of laboratories have demonstrated that different cancers are associated with distinct miR profiles. Given that miRs are stable in serum, our goal is to identify a discrete set of miRs that are breast cancer-specific and which can therefore be employed as disease predicting biomarkers.

PROGRESS: The sample collection and experiments are still ongoing. Submitted for KACST funding.

PROJECT TITLE: **Second Allogeneic Stem Cell Transplantation in Pediatric Patients at KFSH&RC**

RAC # 2081 098

INVESTIGATORS: *Mouhab Ayas, MD (PI), Abdelmoneim Eldali, MSc (BRU I)*

PROJECT DESCRIPTION: Second SCT is now considered a viable option for patients in whom the first SCT was unsuccessful. The two conditions that merit consideration for a second SCT are either graft failure (primary or secondary) or disease relapse in malignant disorders (with or without graft failure).

In the literature, there is now an increasing wealth of data available on second SCT particularly in patients with relapsed leukemia and some studies have even explored the value of reduced intensity conditioning in such patients. This is a retrospective analysis of a cohort of strictly pediatric patients who underwent second stem transplantation for non-malignant disorders at the same institution. In this study, we will try to identify the different factors that may affect the ultimate outcome.

PROGRESS: Data Analysis Completed. A paper resulted from this project.

PROJECT TITLE: **The correlates of male sexual dysfunction in liver transplantation patients and the impact of management**

RAC # 2091 016

INVESTIGATORS: *Raouf Seyam, MD (PI), Abdelmoneim Eldali, MSc (BRU I)*

PROJECT DESCRIPTION: Sexual dysfunction affects 24% of men undergoing liver transplantation. In post transplantation, 32% develop *de novo* sexual dysfunction. The prevalence of erectile dysfunction is 50–95%. The few studies that evaluated the impact of liver transplantation on sexual function have the limitation of lacking objective assessment of its magnitude and missing laboratory assessment of sexual hormonal disturbance and metabolic disorders. Furthermore, a longitudinal report of the outcome of patients with sexual dysfunction management and how this problem affects the quality of life is not available.

There are two components of the study that quantify sexual dysfunction and quality of life using validated questionnaires. The first component is a cross sectional study of sexual dysfunction and quality of life in post transplant male patients. The second component is a prospective study to evaluate the impact of liver transplantation on sexual dysfunction and quality of life.

PROGRESS: In data collection phase.

PROJECT TITLE: **Infection Risk with Noble-Metal Alloy Latex Urethral Catheters in Intensive Care Unit Patients**

RAC # 2091 097

INVESTIGATORS: *Alaa Mukhtar, MD (PI), Abdelmoneim Eldali, MSc (BRU I)*

PROJECT DESCRIPTION: Urinary tract infection (UTI) is the most common hospital acquired infection. The major associated cause is indwelling urinary catheters. Currently there are many types of catheters available. A variety of specialized urethral catheters have been designed to reduce the risk of infection. These include antiseptic impregnated catheters and antibiotic impregnated catheters. Other issues that should be considered when choosing a catheter are ease of use, comfort and cost.

The primary objective of this study is to investigate whether Noble-Metal Alloy Latex (Bactiguard) urethral catheters can reduce the incidence of catheter-associated bacteriuria & nosocomial urinary tract infections rate in adult critical care units in King Faisal Specialist Hospital & Research Centre.

PROGRESS: Completed.

PROJECT TITLE: **Related Haploidentical T-Cell Depleted Stem Cell Transplantation in Patients with Fanconi Anemia Lacking Match Related Donors**

RAC # 2101 048

INVESTIGATORS: *Mouhab Ayas, MD (PI), Abdelmoneim Eldali, MSc (BRU I)*

PROJECT DESCRIPTION: Allogeneic Stem Cell Transplantation (SCT) has been established as the only treatment modality that can definitively restore normal hematopoiesis in patients with Fanconi anemia; excellent results have been obtained with matched related donor transplants. In October 2007, we, at KFSH&RC, launched a protocol using reduced doses of Cyclophosphamide in addition to Fludarabine and Rabbit ATG as a conditioning regimen, 12 patients who underwent matched related donor transplants have done well and all 12 engrafted and are alive with no disease. The results of the unrelated cord blood transplantation on the other hand have been rather discouraging; 10 patients underwent unrelated cord blood transplants at KFSH&RC over a 5 year period, using Fludarabine or TBI containing regimens; 4 remain alive, 3 of them are well and with no disease and one is alive with disease; failure of engraftment was the main contributing factor to the demise of the patients. Internationally, the results of unrelated donor transplant (cord or bone marrow) have been equally disappointing with overall survival around 40%. Recently, the place of haploidentical donors for allogeneic SCT in children is gaining credence, with particularly encouraging results in Fanconi anemia patients.

Therefore, in this protocol we propose the use of related haploidentical donors for our patients with FA who do not have matched related donors; patients will receive a conditioning regimen consisting of a single dose total body irradiation (450 cGy), fludarabine (150 mg/m^2) and cyclophosphamide (40 mg/kg). Immunosuppression will be with Rabbit antithymocyte globulin (Fresenius ATG) and cyclosporin. Grafts will be granulocyte colony-stimulating factor (GCSF)-mobilized, CD34+ T-cell-depleted peripheral blood stem cells; patients will be monitored for engraftment, and development of early complications such as GVHD, sepsis, mucositis, hemorrhagic cystitis, and veno-occlusive disease of the liver (VOD). Long term sequelae will also be monitored, particularly the development of post transplant lymphoproliferative disorders (PTLD) and other secondary malignancies.

PROGRESS: In the data collection phase.

PROJECT TITLE: **Patient's Symptomatology in a Palliative Care Outpatient Clinic**

RAC # 2101 053

INVESTIGATORS: *Mohammed Al-Shahri, MD, Abdelmoneim Eldali, MSc (BRU I)*

PROJECT DESCRIPTION: Impeccable assessment and management of symptoms associated with a life-limiting disease is the principal component of palliative care. The outpatient service of the palliative care program in King Faisal Specialist Hospital & Research Centre, Riyadh (KFSH&RC-R), has been operating since the early 1990s. However, the symptomatology of patients seen in the palliative care outpatient clinic in KFSH&RC-R has never been formally studied. This project is a situational analysis research aiming at exploring the prevalence and intensity of common symptoms in the palliative care outpatient clinic at KFSH&RC-R.

PROGRESS: Data Analysis Completed. Papers and abstracts resulted from this project.

PROJECT TITLE: **Outcome of Hematopoietic Stem Cell Transplantation for Autosomal Recessive Osteopetrosis**

RAC # 2101 070

INVESTIGATORS: *Amal Al-Seraihy, MD (PI), Abdelmoneim Eldali, MSc (BRU I)*

PROJECT DESCRIPTION: Hematopoietic stem cell transplantation (HSCT) is often the only practical approach to fatal genetic defects. Autosomal Recessive Osteopetrosis (ARO) also called infantile malignant osteopetrosis, a rare genetic bone disease in which a deficit in bone resorption by osteoclasts leads to increased bone density and secondary Hematopoietic defects. The disease is often lethal early in life unless treated with HSCT. However, recently the dissection of the molecular bases of the disease has shown that ARO is genetically heterogeneous and has revealed the presence of subsets of patients which do not benefit from HSCT.

The aim of this retrospective study is to analyze the outcome of HSCT in Saudi patient with osteopetrosis diagnosed or referred to King Faisal Specialist Hospital & Research Centre between 1993 and 2007.

PROGRESS: In the data collection phase.

PROJECT TITLE: **Epidemiology and Outcome of Febrile Patients Presenting to a Third Line Health Care Facility. A Re-Appraisal**

RAC # 2111 108

INVESTIGATORS: *Johan Breed, MD, PhD (PI), Abdelmoneim Eldali, MSc (BRU I)*

PROJECT DESCRIPTION: Fever is a recognized presenting symptom at the Emergency Room and is often used as a rationale for prescribing antibiotics, even if no clear-cut source is established. This may eventually lead to unjustified use of antibiotics resulting in multi drug resistance in general and extended the spectrum beta loctam resistance and methycillin resistant *Staphylococcus aureus* specifically. This study addresses decision making in the choice of antibiotics and subsequent patient outcome as measured by total hospital stay or additional switch and eventual spectrum of sensitivity of the microorganism for the chosen antibiotic(s).

PROGRESS: In the data collection phase.

PROJECT TITLE: **A Study to Examine the Concordance Between the Neuropsychology Data and the EEG, PET, and MRI Findings in the Pre-Surgery Evaluation of Epilepsy Patients**

RAC # 2061 080

INVESTIGATORS: *Dr Ahmed M. Hassan (PI), Dr Abdulaziz Al-Semari (Co-PI), Dr Mona Al-Khawajah (Co-PI), Wilhelmina Ventura (BRU I)*

PROJECT DESCRIPTION: When patients with intractable seizure disorder are considered for epilepsy surgery for treatment of their disorder, they are evaluated prior to surgery in order to determine the focus of seizure in their brain. The pre-surgery evaluation involves several modalities: MRI, PET, EEG, and

Neuropsychological Evaluation. Agreement among these modalities on a particular brain focus is likely to increase the success rate of the proposed surgery. The study examines the concordance among the modalities used in the pre-surgery assessment of patients considered candidates for epilepsy surgery. The aim is to verify the strengths and weaknesses of neuropsychological evaluation in identifying dysfunctional brain areas of patients with seizure disorder compared to other modalities of assessment, namely the MRI, PET, and EEG studies. The results are expected to guide further research work to enhance sensitivity and specificity of the existing neuropsychological tools.

PROGRESS: Data for 330 cases have been collected and entered into the database. Prepared preliminary statistics for 145 'Comprehensive Epilepsy Program' patients. P. I. finalizing the report.

PROJECT TITLE: **Study of Demographic, Clinical, Pathological, Management, and Outcome Characteristics of Thyroid Cancer at KFSH&RC: A Retrospective Study**

RAC # 2071 071; BESC#: 009/2008

INVESTIGATORS: *Ali Alzahrani, MD (PI); Co-PI: Saud Al-Harthi, MD, Mohamed Al-Harthi, MD, Gamal Mohamed, PhD; Wilhelmina Ventura (BRU I)*

PROJECT DESCRIPTION: The vast majority of patients with thyroid cancer are referred to KFSH&RC. Once managed at their initial presentation, patients remain on a life-long follow-up due to the high recurrence rate even after many years of initial diagnosis. Based on the well-maintained tumor registry of KFSH&RC, the number of patients referred annually has been gradually increasing. But, because of the excellent prognosis in the vast majority of patients, a large pool of patients are still alive and on follow up either in remission or having persistent/recurrent disease. Currently around 3,000 thyroid cancer patients are on long-term follow-up at KFSH&RC. The hospital continue to receive about 150–200 new cases every year. This large pool of patients provides an excellent opportunity fo the study of the disease in all its aspects. A number of studies on the disease profile have been published from KFSH&RC but, was published around 10 years ago. Since then several changes and evolutions took place in the diagnosis and management of thyroid cancer. The standard of care has become much more uniform matching international standards. With this background we strongly feel that it is time to review our data for the purpose of research and education. We will study a representative sample of patients for their demographic and clinical characteristics, diagnostic work-up, initial and follow-up management and outcome.

PROGRESS: Data for 356 patients seen in 1998 and 1999 have been collected and entered into an SPSS database. About 20 more cases to be added. Preliminary analysis done.

PROJECT TITLE: **Gulf Center for Cancer Registration**

RAC # 2061 022, BESC# 002/2006

INVESTIGATORS: *Kandasamy R, Madouj A, Zahrani A, Hashim S*

PROJECT DESCRIPTION: The Gulf Center for Cancer Registration (GCCR) was established in 1997. The GCCR database, population-based incidence data that include information on both benign and malignant primary tumors, is of the largest aggregations in Asia. Data is compiled from the six national cancer registries representing the six Gulf countries: Kingdom of Bahrain, Kingdom of Saudi Arabia, State pf Kuwait, State of Qatar, Sultanate of Oman and Untied Arab Emirates. The primary objective of the GCCR is to define the population-based cancer incidence of the GCC countries. Future initiatives include supporting early detection, screening programs and epidemiological studies on cancer.

PROGRESS: Both data analysis and presentation for this project have been done in SAS for the purpose of producing population tree graphs for the GCC population.

PROJECT TITLE: **Thromboembolic Disorders Registry**

RAC # 2001 045, BESC# 004/2001

INVESTIGATORS: *Saour J, Mammo L, Moawad M, De Vol E, Aba Al khalil M, Bassil H, El Naggar M, El Sherif M, Subhani S, Shamy E, Obaid W, Hashim S*

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

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

PROJECT TITLE: **Cleft Lip/Palate and Craniofacial Anomalies Registry**

RAC # 991 030, BESC# 007/1999

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

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

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

PROJECT TITLE: **National Family Safety Program**

RAC # 2081 050, BESC# 008/2007

INVESTIGATORS: *Kattan H, Almuneef M, Al Eissa M, Al Mogbil M, Al Hajjar S, Subhani S, Al Ageel S, AL Fantoukh L, Al Sayyari S, Al-Habib A, Al Kuraisi H, Al Meshari M, Al Othman M, Al Salhi S, Al Malki T, Hashim S*

PROJECT DESCRIPTION: Child abuse is a major health problem that has multiple views. It involves moral, social, educational problems, and attachment failure. Using multiple medical, social, and therapeutic approaches with special focus on prevention and specialized support programs, child abuse can be prevented. The initiation of the National Family Safety Registry (NFSR) will help the National Family Safety Program (NFSP) accomplish some of its main objectives, which are to determine the magnitude of the problem in our country, provide our population with an accurate incidence rate of its occurrence, and determine the risk factors encountered in our population in order to plan for a prevention strategy.

PROGRESS: SAS programs have been written for data analysis and presentation for the NFSP Annual/Cumulative Report.

PROJECT TITLE: **Epilepsy Registry**

RAC # 2011 059, BESC# 009/1997

INVESTIGATORS: *Al Semari A, Al Yamani S, Dosari M, Dhalaan H, Chedrawi A, Subhani S, Al Ageel S, Siddique N, Sahar N, Hashim S*

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

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

PROJECT TITLE: **Neuromuscular Disease Registry**

RAC # 2031 053, BESC# 010/1997

INVESTIGATORS: *Bohlega S, Al Dhalaan H, Stigsby B, Subhani S, Yassen I, Sahar N, Hashim S*

PROJECT DESCRIPTION: The Neuromuscular Diseases Registry (NMDR) was established in 1998. It was discontinued in the same year to be resumed in September 2003. The registry is a coordinated collaboration between the departments of Neurosciences and Biostatistics, Epidemiology and Scientific Computing (BESC). It is designed for the collection, processing, management and analysis of data on NMD patients. The nature and magnitude of these diseases are unknown in the Kingdom. Also their incidence and prevalence are also unknown, but the clinical impression had been that they are more prevalent in KSA than in any other countries. The NMDR at King Faisal Specialist hospital was established to provide health workers with a source of data on the epidemiology of neuromuscular diseases. Also to help them estimate the magnitude of the problem in the Kingdom, and to determine the types of neuromuscular diseases found in the population. Moreover, to obtain patterns of these diseases at KFSH&RC, identify associated risk factors, and to document diagnostic and treatment procedures. This registry is prospective with no sex, nationality, or age exclusion criteria.

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

PROJECT TITLE: **Congenital Heart Disease Registry**

RAC # 991 026, BESC# 011/1996

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

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

noteworthy to mention that the registry is internet-based (web-based), facilitating expansion efforts to other institutions in the Kingdom.

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

PROJECT TITLE: **Neural Tube Defects Registry**

RAC # 991 029, BESC# 018/1999

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

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

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

PROJECT TITLE: **Saudi National Mental Health Servey**

RAC # 2091 093, BESC# 004/2010

INVESTIGATORS: *Al Subaie A, Al Twaijri Y, Al Askary H, Al Manea M, Kessler R, Shahab M, Kattan N, Al Fantoukh L, Siddiqui B, Subhani S, Gabr A, Hashim S*

PROJECT DESCRIPTION: Mental Health Disorders are a major public health problem worldwide, affecting people of all ages, cultures and socio-economic statuses (Baumesiter & Martin, 2007). It is estimated that 450 million people globally have mental disorders. The concern about the disparity between mental health service demand and supply led the World Health Organization (WHO) to start the World Mental Health (WMH) Survey Initiative in collaboration with Harvard University (Kessler & Ustun, 2004). The WMH has been conducted in 26 countries to identify the prevalence, risk factors, prognosis and treatment outcome of mental disorders. Saudi Arabia has launched the Saudi Mental Health Survey (NMHS) in accordance with the WMH Survey. The objective of the study is to estimate the psychiatric morbidity in different regions in Saudi Arabia and magnitude of disability caused by it. The NMHS will be a population-based, epidemiological survey which will be administered to a nationally representative sample of Saudis living in urban and rural areas. We propose a sample of 10,000 participants; males and females above the age of 15, whom will be selected randomly from each household. This sample will cover 13 regions in the Kingdom. A face-to-face interview will be conducted in the homes of the participants by WMH certified teams. The interviewing method will be gender specific. During the interview, the CIDI 3.0 questionnaire, developed by Harvard University, will be administered. A team of Saudi physicians and translators have translated the questionnaire. Subsequently, it has been revised by an expert panel. This study is important in providing vision for clinicians and health policy makers to establish relevant preventive, therapeutic, and rehabilitation services in the Kingdom.

PROGRESS: The pilot study was completed successfully. At present, we are in preparation phase for production.

PUBLICATIONS

BOOK CHAPTER

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ABSTRACTS

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SERVICES

The BRU has been involved wide variety of services which include the following:

CONSULTATION AND DATA CLINICS SERVICES

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

Biostatistical services (hypothesis formulation, study design, power and sample size determination, survival analysis, data analysis and interpretation), Statistical Genetics and Genomics (microarray data analysis for gene expression data, exon array data and copy number variation experiments, pathway analysis, functional, and network analyses and others), Methodological advice, grant application (statistical plan/write-up/grant section), and publication (analysis, re-analysis, review). The list of our clients includes but not limited to:

- Clinical Departments (Pathology, Oncology, Urology, Heart Institute, Medicine, Pediatrics Oncology, Pharmacy, Surgery). Quality Resource Management (QRM), Office of Research Affairs (ORA), Annals of Saudi Medicine. Ministry of Health (MOH), Field Epidemiology Training Program (FETP), King Saud University (KSU) and other hospitals.
- Research Centre (Genetics, BMR, Molecular Oncology, Stem Cell, Cardiovascular Research Program, and others), Gulf Cancer Center, CCC.

SERVICES AS COMMITTEE MEMBER AND REVIEWER

- Services as a judge for the evaluation of the scientific projects at Science and Engineering Projects Competition and national Olympics by King Abdulaziz and his Companions Foundation for Giftedness and Creativity and Mawhiba
- Services as reviewer for well recognized international journals, such as *Gastroenterology*, *Genomics*, *BMC Genomics*, *IEEE Transactions on Antennas and Propagation*, *Turkish Journal of Electrical Engineering and Computer Scienc*e, *PLoS One* and others.
- Services as reviewer for KACST proposals.

- Services as Editorial Board Memberships for International perr-reviewed journals *Genomics* and *PLoS One*.

TEACHING AND TRAINING

Teaching and Training activities in statistical computing and in the use of statistical software packages to improve the statistical knowledge among clinicians, scientist, postgraduate students, fellows and MS/PHD students.

- Teaching in Biostatistics and Mathematics courses.
  - Biostatistics from the Beginning Course.
  - Biostatistics Research Methods course.
  - Business Mathematics course for Medical Secretaries Program.
  - Various other biostatistics courses.

- Training students in summer programs.

Epidemiology Section

HEAD
Yasmin Al Twaijri, PhD

MEMBERS
Abdulrahman Bin Muammar
Farah Aldelaigan, MSc
Mansour Al Joufan, MD *(Joint Appointment)*
Saud Al Shanefey, MD *(Joint Appointment)*
Mona Shahab *(Visiting Staff from PSCDR)*
Feda Altuwaijri *(Visiting Staff from PSCDR)*
Maha Al Eid *(Scholarship Leave)*
Bilal Sohail *(Visiting Staff from PSCDR)*

The Epidemiology Section (ES) within the Department of Biostatistics, Epidemiology and Scientific Computing, is an interdisciplinary research unit, which encompasses a broad range of research specialties. Our mission is dedicated to understanding the patterns and causes of health and disease, and the application of that knowledge in improving the health of populations. The ES is actively involved in collaborative research with other departments at the KFSH&RC, in addition to external institutions from the region and internationally. Research areas include cancer, cardiovascular disease, mental health, disability, diabetes, child and adolescent health, obesity, nutrition, genetic diseases, and women's health. The ES currently has 1 permanent scientist, 2 adjunct scientists, 2 technical staff and 1 admin staff.

Scientists within the ES have strong links to other institutions and programs, serving as advisors, committee members or collaborating co-investigators at King Saud University, Ministry of Health, King Abdulaziz Medical City, Prince Salman Center for Disability Research, Harvard University, University of Michigan, and Saudi Commission for Health Specialties. Scientists within the ES are also involved in capacity development through presenting and participating in lectures, seminars and courses on a variety of topics related to epidemiology and research methodology. Our annual Research Methodology course has received excellent reviews and will be instrumental in capacity building of future researchers. ES scientists have also taught university courses at King Saud University and at the King Saud bin Abdulaziz University for Health Sciences. In addition, the unit's staff have supervised several Saudi graduate students, who have benefited from the experience and knowledge of the ES scientists and their access to ongoing studies.

RESEARCH PROJECTS

PROJECT TITLE: **Saudi National Mental Health Survey**

RAC # 209 1 093

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DATA MANAGER: *Samia Alhashem (Biostatistics Unit)*

PROJECT DESCRIPTION: The Saudi National Mental Health Survey is a collaborative project between the KFSH&RC, Ministry of Health, King Saud University (KSU), King Abdulaziz City for Science and Technology (KACST), Ministry of Economy and Planning, Prince Salman Center for Disability Research and Harvard University. Grant funding for the study has been received from PSCDR/Abraj Capital, KSU and SABIC.

Mental health disorders are a major public health problem worldwide. Besides causing significant impairment to the personal, social and occupational functioning of the individual, there are also significant costs to society in lost worker productivity and utilization of health care resources. Epidemiological surveys of diseases are important for identifying prevalence & risk factors, elucidating phenomenology and studying prognosis and outcome of treatment. It is also important in providing vision for future planning of relevant preventive, therapeutic, and rehabilitation services in the society.

Mental disorders are perhaps the largest class of diseases for which evidence exists of a substantial discordance between societal burden and health-care expenditures. The World Health Organization (WHO) Global Burden of Disease (GBD) Study estimated in the mid-1990s that commonly occurring mental disorders such as major, bipolar disorder, schizophrenia, and substance abuse are among the highest-ranked diseases in the world in terms of disease-specific disability. Safe, effective, and comparatively inexpensive treatments for most of these disorders were available at that time. Yet the proportion of total health-care dollars devoted to the treatment of mental disorders was then, and continues to be, disproportionately low in the vast majority of countries. Concern about this disparity between mental health service demand and supply led the WHO to launch the World Mental Health (WMH) Survey Initiative in an effort to focus the attention of health policy makers on the problems of unmet needs. The approach taken by the WMH is to conduct rigorous general population surveys in nationally representative samples in many countries throughout the world, to generate reputable data from those surveys on the prevalence and societal costs of mental disorders in comparison to common physical disorders, and then to develop data on unmet mental health treatment needs and to speculate on potentially modifiable barriers to recovery.

The Saudi National Mental Health Survey is a large, population-based, epidemiological survey, which will be administered to a nationally representative sample of Saudis living in urban and rural areas. Eligible respondents will be non-institutionalized, ambulatory males and females above 15 years of age, who reside within the 13 administrative regions of Saudi Arabia.

PROGRESS: During the first half of 2011 all activities were focused on the preparation for the pilot study. The pilot training and data collection were conducted from May to June 19, 2011 and aimed at testing all procedures, instruments, administrative and logistical aspects of the planned larger survey SNMHS. The study used the latest, state-of-the-art survey procedures and instruments which have not been used previously in the region.

METHODS: 19 physicians from the Ministry of Health (MOH) attended a 6–day intensive training course to become CIDI certified interviewers. A list of households from throughout the Riyadh city neighborhoods was divided among the interviewers. The interviewers visited the households where they conducted the CIDI interview after randomly selecting 1 male and 1 female respondent from each household. The interview was administered using specialized software on personal laptops which also allowed for implementing several quality control measures.

RESULTS: A total of 74 interviews were completed successfully (response rate 81.6%). All procedures and instruments were used and tested without any problems. However, to improve efficiency there were some minor issues that require modification prior to launching the survey on the national scale: The length of the instrument was found to be longer than expected (3.5 hours on average) and needs to be reduced. Some questions need to be reworded to be clearer. The maps used to find the households were not updated which led to difficulty locating the houses. Advance coordination with MOH is needed to avoid delays in releasing their physician interviewers from clinical duties. Study staff were overworked and necessitates adding additional full time staff.

CONCLUSIONS: The pilot study tested all aspects of the planned Saudi National Mental Health Survey and was a complete success. The randomly selected respondents were very receptive and cooperative. The instruments and procedures were all implemented and completed successfully. Necessary modifications are currently underway to ensure the completion of this project, particularly ensuring the availability of funds for the national phase of the survey, and additional staffing. The success of the pilot test of the Saudi National Mental Health Survey indicates its readiness to be implemented on a national scale, ultimately providing crucial data for health policy m makers and mental health specialists in Saudi Arabia.

PROJECT TITLE: **Riyadh Puberty Study**

RAC # 2081 020

INVESTIGATORS: *Alwan I, Felimban N, Altwaijri Y, Shoukri M, Tamimi W, Almutair A, Tamim H*

PROJECT DESCRIPTION: There has been a progressive, global decline in the age of onset of puberty during the past century. Improvements in medical care and socioeconomic conditions have been implicated as possible explanations for this change. Age of onset of pubertal characteristics are influenced by genetic, geographic, dietary and socioeconomic factors, however clinicians in Saudi Arabia use Western estimates as standards of reference on the local children, due to lack of country-specific norms. In addition, puberty has been linked to plasma cholesterol concentration, which is a major risk factor for cardiovascular diseases. The association between plasma cholesterol and sex hormones is not well established, and has been explored by only a few studies. This study will conduct secondary data analysis using existing data, from a representative cross-sectional sample of Riyadh school children and adolescents who were in grades 1–10 and who participated in the Riyadh Puberty Study in 2006 (N=1267). Our secondary analysis of this existing dataset will aim at determining and establishing the local standard age of onset of pubertal characteristics and its major influencing factors, among children in Riyadh, Saudi Arabia. The associations between plasma gonadal hormones (LH, FSH, estradiol, and testosterone), plasma lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol) and diet will also be elucidated, adding to the current body of knowledge concerning cardiovascular disease risk prevention.

PROGRESS: Additional analysis led to a total of four manuscripts resulting from the study. The study ended and further analysis will continue as resources allow it.

PROJECT TITLE: **Modeling Familial aggregation of cleft lip/plate: A hospital based registry study.**

RAC # 2101 004

INVESTIGATORS: *Ravichandran Kandasamy, Yasmin Altwaijri, Mohamed Shoukri, Aziza Al-Johar, Shazia Subhani*

PROJECT DESCRIPTION: Several studies showed Cleft lip/palate (CL/P) are known to recur in families and the risk of having a second infant with CL/P after given birth to a first infant with same defect varies among women. A high risk of having infants with birth defects can result from maternal or paternal genes, dietary patterns, or long-term exposure to environmental teratogens. A combination of genetic and environmental factors may cause a persistent risk of similar defects in siblings. There has been considerable interest in specifying a genetic model that predicts the familial patterns of recurrence of CL/P. The best fitting single-locus model was found to be as good as the multifactorial threshold (MFT) model in explaining the family data on CL/P and isolated cleft palate collected in Hawaii. However, others showed neither the MFT model nor single-major locus (ML) with random environmental variation model provided a good fit. Genetic analyses of the probands' families were performed under the mixed model with ML and MFT components.

The proposed study is based on the data, without patient's identification detail, from the Cleft lip/palate and Craniofacial Anomalies Registry. This registry was established in 1998 and registers all individuals attending at King Faisal Specialist Hospital & Research Centre with cleft. Objectives of this study are (*i*) to examine similarity among pairs of sibling for each of the two traits (cleft lip or palate), (*ii*) to assess elevation in the risk of disease for a single sib conditional of the fact that the other sib has attained the same disease condition, accounting for the within cluster correlation and (*iii*) to assess the possible effect of consanguinity and gender on the risk of cleft lip/palate. Maximum likelihood estimation method will be used to estimate the model parameters and standard errors of the estimates will be derived.

PROGRESS: Final Progress Report submitted to the Office of Research Affairs (ORA) as follows:

INTRODUCTION: Focus of this project is influence of consanguinity on occurrence and recurrence of orofacial cleft.

MATERIAL AND METHODS: All patients diagnosed with cleft lip or cleft palate or both and registered since June 1999 till December 2009 were included in this study. Patients were classified into two distinct groups: cleft lip with or without cleft palate (CL+P), and isolated cleft palate (CP). Chi-square test was used to test independence of variables. Intracluster correlation coefficient was estimated to assess the degree of correspondence between siblings.

RESULT: Of 1,171 total patients, CL+P were more common (749; 64.0%) than CP (422; 36.0%). Male predominance in CL+P (1.5:1), and a female predominance in CP (0.9:1) was observed ($p<0.0001$). About 30% reported to have family history of clefts and first degree relatives, especially siblings, were affected mostly. More patients with CL+P has family history of cleft than CP (33.6% vs. 22.0%; $p<0.0001$). More than half (637; 54.4%) of our patient's parents were consanguineously married and was seen more in CP (55.9%) than CL+P (53.5%) patient's parents. More history of orofacial cleft was seen in the family of consanguineously married (34.2%) than non-consanguineously married (25.8%), $p=0.003$ and the significance persist both among CP and CL+P group. However, the recurrence in sibling was not different between consanguineous and non-consanguineous marriages. The observation that more subjects with CL+P than with CP reported to have a member in the family affected with orofacial cleft despite that more consanguineous marriages observed in CP than CL+P but more history of cleft was found in consanguineous marriages than not related marriages, might be considered interesting. No families had two affected parents; recurrence of cleft in more than one offspring was higher among parents who had cleft than who do not had (51.4% vs. 11.4%; $p<0.0001$) and this difference persists both in CL+P and CP group. Except a significant male predominance ($p=0.04$) observed in CP group among consanguineously married parents there exists no difference in gender with respect to family history of orofacial cleft or parental consanguinity or having more than one sibling.

CONCLUSIONS: Formulation of public health program including education about the anticipated genetic

consequences is a necessity in this population with a high degree of consanguinity.

PROJECT TITLE: **Spatial-temporal analysis of breast cancer incidence in Saudi Arabia**

RAC # 2101 008

INVESTIGATORS: *Ravichandran Kandasamy, Mohamed Shoukri, Yasmin Altwaijri, Shouki Bazarbashi, Haya Al-Eid, Shazia Subhani*

PROJECT DESCRIPTION: Incidence of cancer may vary within a country and overtime because of previous differences in exposure to risk factors or introduction of new diagnostic methods or interventions for early detection. Understanding spatial relationships of health and illness is important as this may help in identifying new exposure hypotheses that warrant future epidemiologic investigations, also enable more timely interventions. All the reports published, so far, by Saudi Cancer registry shows an increase in incidence of breast cancer and the age adjusted incidence rates are higher in some geographic areas than in other areas, however, an accepted protocol for spatial or temporal analysis of these data is lacking.

This study is an observational epidemiological investigation of breast cancer incidence in Saudi Arabia. It aims to examine variations of incidence over a twelve year period using both purely spatial and space-time models. The specific objectives are (*i*) to determine whether the observed geographical variations in incidence rates are random or represent statistically significant deviations from randomness, (*ii*) to determine whether the apparent excesses are stable over time, or are temporary, and (*iii*) to determine whether the excess incidence can be accounted for by covariates such as age, marital status or stage of the disease.

PROGRESS: Final Progress Report was submitted to the Office of Research Affairs (ORA) as follows:

INTRODUCTION: Incidence of cancer may vary within a country and overtime because of previous differences in exposure to risk factors or the introduction of new diagnostic methods or interventions for early detection. Breast cancer is the most common cancer among women worldwide and also in Saudi Arabia. All the reports published, so far, by the Saudi Cancer Registry shows an increase in incidence of breast cancer and the age adjusted incidence rates were higher in some geographic areas than in other areas. This study examines whether the observed geographical and temporal variations in the incidence of breast cancer in the Kingdom is random or represents statistically significant excesses, as such it is not yet known.

MATERIAL AND METHODS: This study is based on all the invasive breast cancer cases diagnosed between 1994 and 2006 among Saudi women (n=8,395) from Saudi Cancer Registry (SCR). The SCR has been collecting information on cancer patients since 1994 by active method, maintains the highest standards for the data quality and completeness. The female census population by five year age group for the 13 administrative regions of Saudi Arabia was obtained from the Central Department of Statistics & Information website and yearly population was estimated. Patient's usual address of residence at the time of their diagnosis was used to aggregate them in to a geographical unit (regions). In this study, a 'cluster' was defined as a geographic area with significantly elevated risk within the study region as compared to other regions.

The age adjusted incidence rate (using world standard population) was calculated by year of diagnosis for each regions of Kingdom. SaTScan (version 9.1.1), software for the Spatial and Space-Time scan test statistic, was used to explore whether spatial clusters of breast cancer exist in the study area and also to determine whether the reported clusters were long term or temporary. The Generalized Linear Mixed Models (GLMM) and Generalized Linear Models (GENMOD), available in SAS software (for Windows, version 9.3), were used to identify the variability of incidence. Any p value < 0.05 was considered as significant.

RESULTS: Age of study subjects ranged from 13 to 107 years (mean 48.4 years; SD 13.5). Majority were married (5293; 63.0%), more than three quarter (6499; 77.4%) were ductal carcinoma. Makkah region had more number of cases (2347; 28.0%) followed by Riyadh (2225; 26.5%), Eastern (1736; 20.7%), Madinah (490; 5.8%), Qassim (350; 4.2%), Asir (333; 4.0%), Jazan (202; 2.4%), Tabuk (187; 2.2%), Hail (153; 1.8%), Jouf (108; 1.3%), Baha (78; 0.9%), Najran (70; 0.8%), and Northern (69; 0.8%). Because of incomplete address information 47(0.6%) cases could not be assigned to any region. The incidence increased from an annual rate of 7.0 per 100,000 in 1994–1998 to 10.9 per 100,000 during 2004–2006. Both autoregressive and compound symmetry correlation structure of GLMM identified that most of the variability in the data is coming from variability among cities (Region = 0.02431, and City within region = 1.52; p<0.0001), GENMOD with compound symmetry correlation structure estimated a correlation of 0.89. In a purely spatial analysis, the spatial scan statistic identified 4 regions (Asir, Baha, Jazan, and Najran) with significantly (p<0.0001) low incidence rates and 2 regions (Riyadh and Eastern) where rates were significantly (p<0.0001) high. Further, the space-time analysis identified same geographic areas that deviated significantly (p<0.0001) from randomness: 2001 to 2006 with higher breast cancer incidence rates in Riyadh and Eastern region than expected; 1995 to 2000 lower than expected in Asir, Baha, Jazan, and Najran region.

CONCLUSIONS: Breast cancer incidence has increased steadily in Saudi Arabia. The geographical variation of breast cancer incidence, using precise geographical coordinates, was observed among Saudi women over the study period. Results of this study are useful in identifying new exposure hypotheses that warrant future epidemiologic investigations; also enable tools for developing cancer control and prevention programs, ranging from education to increased screening, and more facilities.

PROJECT TITLE: **Impact of Tube Feeding on Aspiration Pneumonia**

RAC # 2091 061

INVESTIGATORS: *Muneera Al-Bugami, Yasmin Altwaijri*

PROJECT DESCRIPTION: Aspiration pneumonia (AP) is a common cause of respiratory morbidity and mortality in elderly and debilitated patients. Aspiration pneumonia is an inflammation of the lungs and bronchial tubes caused by inhaling foreign material (usually foods, liquids, or stomach contents) into the lungs. Without treatment, aspiration pneumonia is associated with a high incidence of cavitation and abscess formation, empyema, acute respiratory distress syndrome, and respiratory failure. Previous studies have shown an incidence of AP as high as 30% in an elderly population. However, AP is a potentially preventable illness. Prevention of AP is one of the most cited reasons for using the feeding tube in elderly and frail patient populations, however the evidence has been insufficient and conflicting. The aging population globally necessitates broadening research in this area. For Saudi Arabia specifically, the literature reflecting tube feeding practices is lacking. This study aims at assessing the prevalence of AP among patients at a tertiary care hospital in Saudi Arabia along with indications, complications and outcomes over a 5 year period.

Aspiration pneumonia (AP) is a common cause of respiratory morbidity and mortality in elderly and debilitated patients. Aspiration pneumonia is an inflammation of the lungs and bronchial tubes caused by inhaling foreign material (usually foods, liquids, or stomach contents) into the lungs. Without treatment, aspiration pneumonia is associated with a high incidence of cavitation and abscess formation, empyema, acute respiratory distress syndrome, and respiratory failure.

Studies have suggested an aspiration pneumonia incidence of approximately 30% in the nursing home population. Aspiration pneumonia is a potentially preventable illness.

Tube feeding is a recognized method for nutritional support in patients known to have difficulty in swallowing due to: dementia, brain stroke and others. The tube is placed percutaneously through a stoma

created on the abdomen (gastrostomy or jejunostomy), using endoscopic or radiological techniques.

Interrupting the cycle of feeding, aspiration and subsequent pneumonia is one of the most commonly cited reasons for using the feeding tube. Use of feeding tubes to prevent aspiration pneumonia in hospitalized population of frail elderly individuals need evaluation. There is insufficient information on the effectiveness of tube feeding in preventing AP. No randomized clinical trials have been conducted about enteral tube feeding, however, considerable evidence from studies of weaker design strongly suggest that tube feeding does not reduce the risks of death, aspiration pneumonia, pressure ulcers, other infections, or poor functional outcome.

Despite the benefit of the enteral route for maintaining proper nutritional status, complications have been reported in tube-fed patients. The use of feeding tubes in patients with aspiration problems was associated with a greater incidence of pneumonia and a higher mortality secondary to pneumonia.

Despite the inconclusive evidence and the ongoing controversy about the effectiveness of tube feeding, the use of feeding tubes has continued to increase in older aged patients. The aging population globally necessitates broadening research in this area. For Saudi Arabia specifically, the literature reflecting tube feeding practices is lacking. This study aims at assessing the prevalence of AP among patients at a tertiary care hospital in Saudi Arabia along with indications, complications and outcomes over a 5 year period.

PROGRESS: Data collection is complete. A data entry database is currently being designed to allow for data entry.

Technical Database Core Facility

HEAD
Saleh Al-Ageel

MEMBERS
May Al-Husseini
Lyna Al-Fantoukh *(Scholarship Receipient)*
Fahad Al-Enazy *(Scholarship Receipient)*
Mansoor Baig

Technical databases core facility (TDBCF) is a unit within the Department of Biostatistics Epidemiology and Scientific Computing (BESC). The mission of the TDBCF is to develop and maintain in-house databases of a technical nature that can be used for research purposes or clinical research registries. The facility provides instruction on the use of developed databases and is committed to design and develop databases and registries on request.

TDBCF provides a proactive support of database systems to ensure a stable and efficient data processing environment for our clients. TDBCF builds databases and web-based applications that serve as effective tools for data retrieval, analysis, planning, and decision support. Our database development is web-centered for internet and intranet development.

APPLICATIONS (DEVELOPED/BEING-DEVELOPED YEAR 2011)

PRIMARY-IMMUNO DEFICIENCY REGISTRY

TDBCF have completed and are in a phase of production implementation for a new registry for Primary-Immuno Deficiency. A registry of Kingdom of Saudi Arabia residents with chronic granulomatous disease (CGD) was established in 2010 in order to estimate the minimum incidence of this uncommon primary immunodeficiency disease and characterize its epidemiologic and clinical features. The minimum estimate of birth rate is between 1/200,000 and 1/250,000 live births for the period 1980–1989.

It has been developed using a Microsoft web based platform (.NET Technology), with the latest tools available making it a robust application, Special effort has been put in to it to make the UI as user friendly as possible, The database design is scalable and well contained to give this application a great user experience.

RARE DENTAL DISORDERS REGISTRY

- The Rare Dental Disorders Registry (RDD) of the King Faisal Specialist Hospital and Research Centre (KFSH&RC) was established in 2010 as a collaborative effort between the Department of Biostatistics, Epidemiology and Scientific Computing and the Department of Dentistry. The registry aims in collecting patients with the following disorders: Ectodermal DysplasiaPapillon-Lafevre syndrome.
- Amelogenesis imperfecta Dentinogenesis imperfect.
- Cleidocranial dysplasia.

HYPODONTIA/APLASIA

The registry will be the first of its kind in the Kingdom with an extensive coverage on the dental anomalies of patients suffering from rare disorders. With this registry, our researchers and healthcare providers will have an important source of data, enabling them to assess and analyze the results of their therapeutic efforts, to optimize treatment, improve outcomes and reduce complications. The registry will also serve as a database for future research and help answer many important questions in the relevant area of healthcare that will aid the health authorities in allocating resources for treatment and more importantly towards the prevention of the disease.

NEWBORN SCREENING—RESULTS SYSTEM

This application is being used nationwide by al requesting hospitals to search, track and view the New Born screening results, The results of the newborn screening system are generated by the LIMS System in the form of a PDF file and does contain vital information and comments which are directly imbeded on the PDF file, currently the manual system was to send the report by email, or at PO Box or other alternatives, this new system has provided all the requestors a platform to download the results themselves so as to save time and manpower. This system is integrated with the LIMS system and the NBS (PDF file system) so as to make the results searchable. This project consist of 2 modules the first modules copies and checks the folder structure from the NIMBS and bumps the folder in a categorized location on a daily basisA database view for the LIMS system has been created so as to fetch the vital searchable information from the LIMS system and make it available for search. The third module is a web based application where which can create a user for each requestor for logging on to the system and view the results for the screenings taken place at their location. It will also contain an administration module to control the records.

SECOND OPINION SUPER STAR PLATFORM

This is a web based interface that show statistical data and flowchart using Super Star Platform. The data is retrieved from Second Opinion database which enable the user to enter and edit data.

SAUDI HEART ASSOCIATION MEMBERSHIP MGT. SYSTEM

The Saudi Heart Association had a requirement to have a membership management system where they can store all the member details which will be updated by the doctor or the administrator on a timely basis. The administrator would be able to add new members and assign them the login privileges, the members would then be able to log on to the

system and update their profile or upload membership renewal documents. It also covers reporting, search and custom list for expired memberships. PHASE 2: will cover the automatic email generation on and before any membership expires, this will be covered soon. It has been developed using the .NET platform with sql server as the backend database

BREAST CANCER REGISTRY

This Registry is an online application developed for the Breast Program, Oncology Centre, to maintain the breast cancer data, it is a multi user application with different user access privileges, Later if required can be scaled to make it a multi-institutional registry.

RESEARCH CENTRE CREDENTIALS COMMITTEE

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

APPLICATIONS RE-DEVELOPED (NEW VERSIONS -2011)

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

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

OLIGONUCLEOTIDE SYNTHESIS ORDERING

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

DESIGN AND DEVELOP WEB BASED APPLICATION FOR SAUDI ARABIA PEDIATRIC HEMATOLOGY ONCOLOGY SOCIETY (SAPHOS)

The Saudi Arabia Pediatric Hematology Oncology Society database is a web-based application developed for the SAPHOS committee residing in the CCC to help in the multi-institution national collaborative study that will be conducted to collect prospectively comprehensive and detailed data on the epidemiology, clinical, laboratory as well as molecular genetics characterization for children with cancer in the Kingdom of Saudi Arabia.

APPLICATIONS (MODIFIED DURING YEAR 2011)

CONGENITAL HEART DEFECTS REGISTRY

The Congenital Heart Defects Registry is a registry designed for the collection, management, and analysis of data on CHDs patients. It was developed by the TDBCF using ASP technology. a new CHD registry has been released. The new CHD provide the users with the same functionality of the old one, including adding/editing/deleting patients' demographics, diagnosis, treatment and follow-up forms. In addition to exporting data, searching the registry, admin features, generating charts, generating different types of reports (progress, annual, error. etc) and enhanced security features.

RE-ENGINEERING THE NATIONAL FAMILY SAFETY REGISTRY

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

CLEFT LIP CLEFT PALATE & CRANIOFACIAL DISORDERS REGISTRY

The Cleft lip/ Cleft Palate registry is designed for the management of data of CLCP patients. It was developed by the TDBCF using ASP technology. In order to provide users with high performance applications and keep up to date with the latest technologies, the CLCP was redeveloped using ASP.Net. The functions of the newly developed CLCP include adding/editing/ deleting patients' forms, searching for specific data, exporting data and generating charts, and reports.

BIOTECH PROJECT MANAGEMENT SYSTEM FOR SCIENCE & TECHNOLOGY

This is a project built for the Research Centre administration / Finance for handling all the biotech projects with KACST. It is a project management tool for the principle investigators, co-investigators, RC finance and admin to manage their project from a financial perspective. This Idea is intended to be upgraded soon to make this system go nationwide for all research projects

MIDDLE EAST CHILDHOOD CANCER ALLIANCE (MECCA)

Sixteen countries' pediatric oncologists from middle-east region announced an alliance against childhood cancer in November 2000. The strong interest and commitment of this alliance would be the improvement of the diagnosis, management of diagnosis and quality of life of the children afflicted with cancer in the region. It was decided that the coordinating office in KFNCCC&R, Riyadh, Saudi Arabia supervised by MECCA Coordinator would assume absolute confidentiality and safety of data collected. An application is being designed and developed by TDBCF that would provide secured shared access to centralized data of MECCA project through Internet.

ONGOING APPLICATION (USERS SUPPORT & MAINTENANCE)

BREAST CANCER SAMPLES MANAGEMENT APPLICATION

A Web-based application developed for Breast Cancer Research Unit, BMR department, to manage their samples data. Application has features to store/ retrieve demographic disease, medical history and samples information. Barcode can also be generated online. Application also provides features to store/ retrieve picture by allowing the user linking of those pictures to either patient or specific sample. Information about child samples and isolated material can also be managed within this application.

ARABIAN HORSES WEB APPLICATION

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

NEUROPSYCHOLOGY DATABASE

Neuropsychology Database is a web-based application and it was developed for keeping patients records in order to refer to them later. Neuropsychology provides several functions. It allows managing the patients by adding, updating and deleting them. Search for patients is designed to generate a list of patients having the same criteria. This application generates Neuropsychology data reports and provides Export feature for data exporting. It gives the privileges to the user with administrative level to managing the user of the system.

BILLING DATA MANAGEMENT SYSTEM

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

- To keep track of all rendered services, supplied products and laboratory test performed.

- To keep track of all bills to the clients and receipts against those bills.

THROMBOEMBOLIC REGISTRY (TEDR)

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

NEURAL TUBE DEFECTS REGISTRY (NTDR)

The Neural Tube Defects Registry is a national registry that serves as a source of data on NTD. The currently running application is developed by the TDBCF using ASP Technology. In order to provide users with high performance applications and keep up to date with the latest technologies, the NTDR is redeveloped using ASP.Net. The functions of the newly developed NTDR include adding/editing/deleting patients' forms, searching for specific data, exporting data and generating charts. In addition to the enhanced security features that manage the use of the system and maintain the confidentiality of patients' information

EPILEPSY REGISTRY

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

THERMO LUMINISCENT DOSIMETRY (TLD)

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

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

NATIONAL LABORATORY FOR NEWBORN SCREENING

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

SAUDI THROMBOSIS AND FAMILIAL THROMBOPHELIA REGISTRY

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

THROMBOEMBOLIC DISORDERS REGISTRY

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

CYCLOTRON MAINTENANCE DATABASE

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

NEUROMUSCULAR DISEASES REGISTRY

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

RESEARCH CENTRE GRANT LEAVE DATABASE

Leave system is a web-based application and it was developed for RC Admin to manage the Grant Leave. This application provides the ability to enter Grants, update their information, delete them and searching for Grant with a given criteria. It also adds leave requests for a specific grant and it allows viewing Inquiries such as Leave Request and leaving situation. It grants the user with administrative level the privileges to managing the users of the system by adding, updating and deleting them.

USERS' TRAINING

TDBCF Section is committed to provide users training sessions at the completion of each application.

Professional Training

TDBCF TRAINEES

TDBCF understands the importance of training and development and is dedicated to provide the best possible way of induction training for new staff members and grants. The best method of training is supposed to be the induction training where in the training covers the practical aspects of the development methodology in a real-time scenario.

The Trainee is made a part of a current ongoing project where he/she passes though the real project development cycle so as to get a feel of actual software design and development which is not limited to just the theoretical understanding.

SUMMER TRAINING

TDBCF provided summer training for three computer information system graduated candidate.

The Candidates were given a task of developing a .NET search application which would query various disease registries based on the medic al record number.

This application should help identify patients being registered under multiple disease registries.

BASIC OBJECTIVES

The search application would have its own login privileges and user security

- A generalized database needs to be build to unify the common available variables based in various registries.
- Each disease registry would be registered in this database along with the Sql database server and name it points to.
- Variable mapping created for each registry to map its searchable elements
- Search forms were build accordingly to search patients based MRN or other search criteria
- This idea can be further refined to provide a real-time multi–ailment search for patients based on the registry data available.

Registries Core Facility

HEAD
Shazia Naz Subhani, MSc

MEMBERS
Nadia Dessouky, MD
Ahsan Yaseen, MPH
Mohamed Nasser Ibrahim
Ebtisam Al-Jarba
Ehsan El Shamy
Jawad Afzal, MD
Hanaa Abdulghany
Hala Al Assiry
Nada Bawyan
Najah Finjan
Abobakr Ba Fadhl

Throughout the year 2011, registries scope has expanded not only in terms of collaborations but also in terms of planning and developing new registries namely Chronic Diseases Registry and Organ Transplantation Registry that is inclusive of Lung, Liver, Pancreas, Kidneys and GI System. Currently, RCF is administering several hospital based, regional and national registries. Members of RCF were involved trainings users from various collaborating hospitals on national level. Data recorded and reported from individual registries were tabulated and presented as cumulative and/or annual reports. All reports are available under a common link *http://rc.kfshrc.edu.sa/rcf*. Comprehensive electronic libraries for individual registries were created and uploaded for reference under the same link. Several data requests for the spin-off projects, after necessary documentation, were furnished to researchers. Several presentations on the research projects were made along with co-authorships on research papers.

Additionally, in 2011 the effective use of health care technologies lead several registries to get projected; using published data; on the dynamic health statistics platform. KFSH&RC is a pioneer in the establishment of disease registries and keeping in view the strategic planning for research activities efforts are in place to bring all published registries data under this dynamic platform. The dynamic enhances the importance of research data collected over the years for the on-going registries by providing instant tabulations, graphs and maps. This will not only satisfy the research inquiries but will also play a major role in the administrative decision and public awareness for various health problems addressed through the registries. The platform is accessible under *http://altabari.kfshrc.edu.sa*.

CURRENT RESEARCH PROJECTS

PROJECT TITLE: **Congenital Heart Defects Registry (CHDR)**

RAC # 99 1026

INVESTIGATORS: *Zohair Halees MD, Mansour Al Jufan MD, Futwan Al Mohanna PhD, Mohamad Shoukri PhD, Ahmad Omrani MD, Mamdouh Al Ahmadi, Abdullah Al Shely, Shazia Naz Subhani MSc, Nadia Dessouky MD*

PROJECT DESCRIPTION: The congenital heart defects registry of the King Faisal Specialist Hospital and Research Centre (KFSH&RC) was established in 1998 on hospital level as research collaboration between the Department of Biostatistics, Epidemiology and Scientific Computing and the King Faisal Heart Institute. Since the year 2003 the Congenital Heart Defects registry is a multi-institutional collaboration on both regional and national levels. Hospitals on board are; King Faisal Heart Institute at KFSH&RC, Riyadh. Prince Sultan Cardiac Centre, Riyadh. Al-Dammam Maternity & Children Hospital. King Fahad Medical City, Riyadh. Cardiovascular Department at KFSH&RC Jeddah. King Abdulaziz Cardiac Center at King Abdullah International Medical Research Centre, NGHA.

The Congenital Heart Defects Registry is using web-based software with the latest state-of-art technology, designed for the collection, processing, management, and analysis of data on CHD patients. Being an internet application all activities are real-time.

PROGRESS: Cumulative report for (1998–2010) submitted. King Abdulaziz Cardiac Center at King Abdullah International Medical Research Centre, NGHA, Riyadh joined the collaborative work in September 2011. User training conducted successfully for NGHA.

PRESENTATIONS: "Features and Concepts: Saudi Congenital Heart Defects Registry", Oral Presentation during the 22nd scientific meeting of the Saudi Heart Association, February 2011, Riyadh

Statistics for all year cases as of December 31, 2011 is:

Collaborating Hospitals	New cases	Follow up cases	Diagnosis	Treatment
(KFSH&RC Riyadh, PSSC, Riyadh, MCH, Al-Dammam, KFSH&RC, Jeddah, NGH, Riyadh	22,178	52,911	17,917	20,223

Statistics for year 2011 is:

Collaborating Hospitals	New cases	Follow up cases	Diagnosis	Treatment
(KFSH&RC Riyadh, PSSC, Riyadh, MCH, Al-Dammam, KFSH&RC, Jeddah, Cardiac Center, NGH, Riyadh	3,639	4,064	1,629	1,531

Data projection for the published CHD report uploaded on the Health Statistics Platform.

FUTURE DIRECTIONS: Maintain the main objectives of the registry. Extend CHDR collaborative work with other regional and national hospitals.

PUBLICATIONS: Multi-Institutional Cumulative Report (1998–2010).

Data projection for the published CHD report uploaded on the Health Statistics Platform.

FUTURE DIRECTIONS: Maintain the main objectives of the registry. Extend CHDR collaborative work with other regional and national hospitals.

PUBLICATIONS: Multi-Institutional Cumulative Report (1998–2010)

PROJECT TITLE: **Neural Tube Defects Registry (NTDR)**

RAC # 99 1029

INVESTIGATORS: *Essam Al Shail MD, Mohammad Al Abdulaaly MD, Zayed Al Zayed MD, Mohamad Shoukri PhD, Hoda Kattan MD, Wesam Kurdi MD, Nadia Sakati MD, Shazia Naz Subhani MSc, Ihsan Yassen MPH*

PROJECT DESCRIPTION: Neural Tube Defects refer to a group of lesions that occur at various positions along the spinal cord, which are ultimately due to a defect in the closure of the neural groove to form an intact neural tube. Anencephaly, spina bifida and encephalocele account for almost all NTD's. The King Faisal Specialist Hospital and Research Centre established in March 2000 a registry for all patients with neural tube defects presenting to the hospital. The registry is a coordinated collaboration among the departments of Neurosciences, BESC, Pediatrics, Orthopedics, urology, and Obstetrics and Gynecology. The purpose of the registry is collection, management, and analysis of data belonging to patients diagnosed with NTD and presenting to KFSH&RC. Active data acquisition and registration is on-going from KFSH&RC and the collaborating hospitals; KFSH&RC, Jeddah, Disabled Children Association, Riyadh & Jeddah, King Saud Medical Complex, Riyadh, and Al Qunfudah General Hospital.

PROGRESS: Data audited prior to annual report data tabulation. On-going collaboration with regional hospitals.

Statistics for all year as of December 31, 2011 is:

	New cases	Follow up
KFSH&RC + Collaborating Hospitals	685	367

Statistics for year 2011 is:

	New cases	Follow up
KFSH&RC + Collaborating Hospitals	42	50

FUTURE DIRECTIONS: On-going collaborations with hospitals which are in agreement with the registry expansion plans. New collaborations.

PUBLICATIONS: Eleventh Annual Report with Registrations from October 01, 2000 untill December 31, 2011.

PROJECT TITLE: **Epilepsy Registry**

RAC # 2011 059

INVESTIGATORS: *Abdulaziz Al Semari MD, Aziza Chedrawi MD, Hisham Al Dhalaan MD, Ibrahim Thubaiti MD, Salah Baz MD, Suad Al Yamani MD, Shazia Naz Subhani MSc, Najah Aftab Siddiqui MSc Mohammad Nasser Ibrahim, BS*

PROJECT DESCRIPTION: Epilepsy is a disease that affects people of all ages, races and nationalities. Symptoms, frequency, intensity and types of seizures vary greatly from person to person. According to the World Health Organization up to 5% of the world population have or will at some time suffer from epilepsy in their lifetime. In Saudi Arabia, the incidence or prevalence of epilepsy is unknown.

Epilepsy Registry is a collaborative undertaking between the Department of Biostatistics, Epidemiology and Scientific Computing and the Department of Neurosciences at KFSH&RC. The registry aims at systematic collection, management and analysis of data on patients with epilepsy (pediatric and adult) who present to KFSH&RC, regardless to their nationality, starting 01 April 2000. Sources of data include medical records and face-to-face interviews with the patient (or guardian). Registry is expected to provide an important source of data to enable health care workers to estimate the magnitude and impact of epilepsy on the society and to assess the result of the therapy. Hence, improvements of patient care and better health care planning (services and research).

PROGRESS: Data audited prior to cumulative report data tabulation. Registry Data Presentations as follows: Clinical Features and Surgical Outcome of Hemimegalencephaly in Saudi Arabia. S. Al Yamani, I. Thubaiti, Aldhalaan, S. Baz, A. Al-Semari,

F. Almuhaileb, H. Alhindy. 65th Annual American Epilepsy Society Meeting Baltimore 3–6 December 2011. "Vagus Nerve Stimulation: Quality of Life and Patient's Satisfaction" F. A. Al-Otaibi, S. Baz, A. Abujaber, A. Alsemari, 65th Annual American Epilepsy Society Meeting Baltimore 3–6 December 2011.

Statistics for all year as of December 31, 2011 is:

	New cases	Diagnosis	Surgery
Collaborating Hospitals	3682	3330	466

Statistics for year 2011 is:

	New cases	Diagnosis	Surgery
Collaborating Hospitals	268	219	35

FUTURE DIRECTIONS: On-going collaboration with Riyadh Military Hospital, King Abdulaziz Medical City/King Fahad National Guards Hospital-Riyadh and KFSH&RC, Jeddah, King Fahad Medical City-Riyadh

PUBLICATIONS: Multi-institutional Annual Epilepsy Registry Report (2010)

PROJECT TITLE: **Cleft Lip / Palate and Craniofacial Anomalies Registry (CLCPR)**

RAC # 991 030

INVESTIGATORS: *Aziza Al Johar MD, Essam Al-Shail MD, Abdulaziz, Kandasamy Ravichandran PhD, Shazia Naz Subhani MSc, Ebthisam Al Jarba BA*

PROJECT DESCRIPTION: Clefts of the lip and Palate are one of the most common human malformations of the face. Since CLP is a complex and chronic disability lasting from birth through adulthood and requiring long term coordinated treatment, it was particularly important to have a registry for this disease. Seeing the necessity, KFSH&RC designed a registry for this purpose in the year 1999 to provide a database on cleft lip/cleft palate patients at the hospital and use the data collected to enhance patient care by justifying the allocation of resources based on need.

PROGRESS: Data validation and auditing.

Presentations on registry data as follows:

- Consanguinity and Occurrence Pattern of Cleft Lip/Palate: A hospital-based registry study, RiyadhReview Craniosynostosis cases by Dr. AlShail and Dr. Anwar UL Haq.

Statistics for all year as of December 31, 2011 is:

	New cases	Diagnosis coding	Treatment coding
King Faisal Specialist Hospital & RC	1532	2089	4612

Statistics for year 2011 is:

	New cases	Diagnosis coding	Treatment coding
King Faisal Specialist Hospital & RC	114	149	346

FUTURE DIRECTIONS: Collaborations.

PUBLICATIONS:

- Cleft Lip/Palate and Craniofacial Anomalies Registry Cumulative Report 1999–2010.2. Ravichandran K, Shoukri M, Aljohar A, Shazia NS, Al-Twaijri Y, Al Jarba I. Consanguinity and occurrence of cleft lip/palate: A hospital-based registry study in Riyadh. *Am J Med Genet A*. 2012 Feb 2. doi: 10.1002/ajmg. a. 344323.
- Aziza A, Kandasamy R, Shazia S. Pattern of craniofacial anomalies seen in a tertiary care hospital in Saudi Arabia. *Ann Saudi Med*. 2011 Sep-Oct;31(5):488–93.

PROJECT TITLE: **Thromboembolic Disorders Registry (TEDR)**

RAC # 2001 045

INVESTIGATORS: *Abdulaziz Al Harthi MD, Abimbola Akomolafe MD, Jalal Saour MD, John Breed MD, Habib Bassil MD, Layla Mammo MD, Muneera Al Bugami MD, Mohamed El Karouri MD, Abdelazeim Elamin MD, Ulrike Laudon MD, Zahid hussain MD, Mohamad Shoukri PhD, Shazia Naz Subhani MSc, Ehsan El-Shamy BSN*

PROJECT DESCRIPTION: Thromboembolic disorders are important causes of mortality and common causes of morbidity in the Kingdom of Saudi Arabia. The true incidence of these disorders in the Kingdom is not known but it is unlikely to be less than that reported in the Western countries. TED Registry is to serve as a repository of data specifically for patients with Thromboembolic disorders. This will enable contributors to the registry to analyze outcomes of management, to optimize treatment and improve outcomes. All patients referred to the Thromboembolic Service for anticoagulation therapy at KHSH&RC are included in the registry. The Thromboembolic Disorders (TED) Registry of King Faisal Specialist Hospital and Research Centre were established in February 2001 as collaboration between Biostatistics, Epidemiology and Scientific Computing (BESC) Department and Internal Medicine Department. All patients presenting to the Thromboembolic Service in the section of Internal Medicine are registered after getting their informed consent.

PROGRESS: Data audited prior to cumulative report data tabulation.

GRAND ROUND PRESENTATIONS:

- Jalal N. Saour MBChB FRCPI, Atia W. Shereen PhD, Basil J. Saour BSc (Hons) MD, Layla A. Mammo, BSc Pharmacy PhD. CYP2C9 Polymorphism in Normal Saudi Individuals and Patients with Venous Thrombosis and Those Requiring Low Dose Warfarin - A Prospective Study. 13th Annual Research Promotion Day, Dept of Medicine, KFSH&RC, Riyadh, KSA, May 2011.
- J Saour FRCPI, Atiya Sheereen PhD, T. Saour BSc DDS, M Shoukri PhD and L Mamo PhD. Inherited Thrombophilia in Normal Saudis and Those with Venous Thrombosis and Cancer-The Saudi Thrombosis and Familial Thrombophilia Registry. XXIII Congress of the International Society on Thrombosis and Haemostasis, Kyoto, Japan, 23–28 July 2011.

PUBLICATIONS:

- Saour JN, Shereen AW, Saour BJ, Mammo LA. CYP2C9 Polymorphism in Normal Saudi Individuals and Patients with Venous Thrombosis and Those Requiring Low Dose Warfarin–A Prospective Study. XXIII Congress of the International Society on Thrombosis and Haemostasis, Kyoto, Japan, 23–28 July 2011.

Statistics for all years as of December 31, 2011 is:

	New cases	Follow up cases
King Faisal Specialist Hospital & RC	3455	5661

Statistics for year 2011 is:

	New cases	Follow up cases
King Faisal Specialist Hospital & RC	265	1301

PUBLICATIONS:

- Thromboembolic Disorders Registry Cumulative Report (2001–2010).

PROJECT TITLE: **Venous Thrombosis and Thrombophelia Disorders Registry (VTFT)**

RAC # 2001 017

INVESTIGATORS: *Jalal Saour MD, Layla Mammo, Mohamad Shoukri PhD, Shazia Naz Subhani MSc Ehsan El-Shamy BSN*

PROJECT DESCRIPTION: The incidence and prevalence of venous thrombosis (VT) and venous thromboembolism (VTE) and their trend in Saudi Arabia is not known. However, there is a good reason to

suspect that they will increase as the population ages, patients undergo and survive more major surgery, survive myocardial infraction, CVA and chemotherapy for malignancies. Thrombosis and Familial Thrombophilia Registry was initially initiated by the Coagulation Research Unit at the Department of Biological and Medical Research (now closed), Research Centre KFSH&RC in collaboration with the Registries Core Facility in Biostatistics, Epidemiology and Scientific Computing Department and Thromboembolic Service, Department of Medicine at the King Faisal Specialist Hospital and Research Centre, Riyadh. Now that the Coagulation Research Unit laboratory is non-functional, further genetic testing has stopped. However, we did get most of the information we set out to do i. e. which genetic factors are at risk for VT in Saudi population. The registry project is now approved as a national open registry with a name Saudi Thrombosis and Familial Thrombophilia Registry (S-TAFT).

PROGRESS: As of December 31, 2011 total counts in the database is: 1489 cases. For year 2011 patients registered are: 124 cases.

FUTURE DIRECTIONS: National collaborations.

PROJECT TITLE: **Neuromuscular Disease Registry (NMDR)**

RAC # 99 1029

INVESTIGATORS: *Mohammed Al Muhaizea MD, Saeed Bohlega MD, Bent Stigsby MD, Hisham Al-Dhalan MD, Shazia Naz Subhani MSc, Ahsan Yassen MPH*

PROJECT DESCRIPTION: The nature and magnitude of neuromuscular disease in Saudi Arabia are unknown, but the clinical impression had been that there are more prevalent than in other countries. Also the burden on the medical community to care for these patients is unknown. The NMDR at King Faisal Specialist Hospital and Research Centre, Riyadh was established to provide an important source of data to enable health workers in estimating the magnitude of the problem in the Kingdom, in assessing the results of their therapeutic efforts and to determine the types of Neuromuscular Diseases encountered in the population. Moreover to obtain the incidence, prevalence and patterns of neuromuscular diseases at KFSH&RC, to identify risk factors associated with these diseases and to document the treatment procedures and assessment of treatment outcome. The registry is designed by the BESC Department in collaboration with Department of Neurosciences. It is Prospective and case ascertainment is active.

PROGRESS: Duchenne muscular dystrophy, retrospective study. RAC # 2111049. May 2011. This project utilized data from the registry. Data audited prior to cumulative report data tabulation.

Statistics for all year as of December 31, 2011 is:

	New cases	Diagnosis coding	Treatment cases
King Faisal Specialist Hospital & RC	2880	2880	3473

Statistics for year 2011 is:

	New cases	Diagnosis coding	Treatment cases
King Faisal Specialist Hospital & RC	439	439	430

PUBLICATIONS:

- Neuromuscular Disease Registry 2010, Annual Report.

PROJECT TITLE: **National Family Safety Registry (NFSR)**

RAC # 2081 050

INVESTIGATORS: *Huda Kattan MD, Maha Muneef MD, Majid Al Eissa MD, Shazia Naz Subhani MSc*

PROJECT DESCRIPTION: The NFSP was initiated in November 2005 pursuant to the Royal Decree No. 11471/ MB with a mission to prevent child abuse and domestic violence in the Kingdom. The program

is a collaborative project between different government and non-governmental agencies including the Ministry of Health and other health service providers in the Kingdom that addresses the issue of child abuse and domestic violence. With the increased number of reported case of child abuse, there is a rising need to initiate a national registry of child abuse. Collaboration between NFSP and King Faisal Specialist Hospital & Research Centre is mandated to develop a "state-of-the-art" registry.

PROGRESS:

1. First Report on the National Family Safety Registry published.
2. Registry software updates
3. Data validation
4. Acquired cases as of December 2011: 578

FUTURE DIRECTIONS: Collaborations with Ministry of Social Affairs and other hospitals.

PUBLICATIONS:

- First Report 2010 on National Family Safety Registry.

PROJECT TITLE: **Pan Arab Liver Transplantation Registry (PALTR)**

RAC # 2071 022

INVESTIGATORS: *Professor Mohamed Al-Sebayel MD, Hatem Khalaf MD, Khalil Alawi MBBS, Mohamad Shoukri PhD, Shazia Naz Subhani MSc*

PROJECT DESCRIPTION: In March 2006, the 1st Pan Arab Liver Transplantation Congress was held in Cairo with great success. The meeting witnessed the birth of the Pan Arab Liver Transplantation Society (PALTS). One of the main goals of the Pan Arab Liver Transplantation Society was establishing a Web-Based Pan Arab Liver Transplantation Registry that will help in promoting and encouraging education, research and cooperation in the field of liver transplantation between various liver transplant programs in the Arab World. Keeping in view this goal, in the year 2005 the first of its kind Pan Arab Liver Transplantation web-based registry was designed and developed and became prospective for the King Faisal Specialist Hospital as a part of Phase I of the registry objectives. This registry is a collaborative work between the Department of LTx and Hepatobiliary-Pancreatic Surgery and, the Department of Biostatistics, Epidemiology and Scientific Computing (BESC).

PROGRESS:

1. On-going collaboration with Wade-e-Nyle, Egypt and Cairo University, Egypt.
2. As of December 31, 2011 a total of 689 patients registered in the centralized database.
3. On-going data collection and entry in the registry database.

FUTURE DIRECTIONS: Pan Arab Level Collaborations

PROJECT TITLE: **Rare Dental Disorders Registry (RDDR)**

RAC # 2071 082

INVESTIGATORS: *Adeeb Al Omrani BDS, DMSc, Hans Hansson DDS, Richard Hakansson DDS, PhD, Khalid Al Zoman BDS, MS, Shazia Naz Subhani M. Sc*

PROJECT DESCRIPTION: Congenital Oral Anomalies are a broad category of health conditions that are present at birth and are a deviation from normal anatomic growth, development, or function. There is an urgent need to increase knowledge about oral rehabilitation for people with oral/dental disabilities and new methods for treatment must be developed and evaluated which will lead to better care and will have great influence on the quality of life for people with oral disabilities. In this regard a web-based registry design is under process. The aim of this registry is a multi-disciplinary team approach to enhance the opportunities for individuals from all over the country with rare-oral and facial disorders to get

adequate information, diagnosis and treatment at King Faisal Specialist Hospital & Research Centre.

PROGRESS: 1. Registry web application designed and tested with dummy data. 2. Data capturing and entry on-going

Statistics for year 2011:

	New Cases
King Faisal Specialist Hospital & RC	84

FUTURE DIRECTIONS: Collaborations.

PROJECT TITLE: **Primary Immunodeficiency Registry (PIDR)**

RAC # 2081 111

INVESTIGATORS: *Bandar Al Saud MD, Saleh Al Muhsen MD, Abdulaziz Al-Ghonaium MD, Hmoud Al-Musa MD, Hasan Al-Dhekry MD, Sulaiman Al-Gazlan MD, Hasan Al-Rayes MD, Rand Arnaout MD, Nazeema Elsayed, Mohamad Shoukri PhD, Shazia Naz Subhani MSc Jawad Afzal MD*

PROJECT DESCRIPTION: Primary immunodeficiency are disorders in which part of the body's immune system is missing or does not function properly. To be considered a Primary Immunodeficiency, the cause of the immune deficiency must not be secondary in nature. About 1 in 500 people is born with a primary immunodeficiency. (Wikipedia)Since PIDD are complex and chronic lasting from birth through adulthood and requiring long term coordinated treatment, it was particularly important to have a registry for this disease. Seeing the necessity, KFSH&RC designed a registry for this purpose in the year 2010 to provide a database on PIDD patients at the hospital and use the data collected to enhance patient care by justifying the allocation of resources based on need.

PROGRESS: Since the inception of the registry in May 2010, data abstraction/ acquisition and entry through the web-application are prospective. Cumulative report will be published after data validation and auditing next year.

Statistics till December 31, 2011 is:

	Total Cases
King Faisal Specialist Hospital & RC	219

Statistics from January, 2011 to March, 2012:

	New Cases
King Faisal Specialist Hospital & RC	132

FUTURE DIRECTIONS: National Collaborations.

PROJECT TITLE: **Chronic Diseases Registry (CDR)**

RAC # 2081 050

INVESTIGATORS: *Aneela Hussain, MD, Abdullah Al-Khenizan MD*

PROJECT DESCRIPTION: With the increasing number of patients with chronic diseases like hypertension, hyperlipidemia and diabetes, there is a rising need to initiate a national registry of chronic diseases. Developing this registry will help in compiling huge data of our patients with these chronic diseases. The rationale for developing this registry is to determine the magnitude of chronic diseases encountered in KSA patient population. This will facilitate expanded and improved medical care by monitoring the progress of these patients. Later on additional centres will be allowed to collaborate with the registry so that a national data can be generated as a part of registry expansion plans.

PROGRESS: Registry software design and development. Application tested with dummy data

FUTURE DIRECTIONS: Data Collection, analysis and reporting.

Computer Services Core Facility

HEAD
Parvez A. Siddiqui

MEMBERS
Mashnouf Al-Rowaily
Arnie Tayco
Yousef Hussain
Bandar Al-Khodairi
Michael Edquiban

The computing services core facility (CSCF) is playing a major role by providing information technology support to the Research Centre which is a research projects oriented institution.

The CSCF is primarily a server administration and computing support unit. Services provided by CSCF span the full range of tasks necessary in keeping laboratory and office computers in good operating condition, in addition to ascertaining that data and application servers are performing up to the level of expectation.

The CSCF provides technical assistance to all the Research Units and Core Facilities in the department as well as to all the scientists and clinicians engaged in biomedical research from within the Research Centre and from the hospital as a whole.

TRAINING COURSES

In keeping abreast with developing technologies, CSCF endeavors to acquire technical expertise through a hands-on approach, supplemented by online research work. In addition, and in promoting career advancement, some members of the staff enroll in formal technical courses.

Training and Seminars

1. Resident's Research Day January 18, 2012
2. International Conference on February 27–March 1, 2012
3. Radiation Medicine
4. Security Matters March 18, 2012
5. Scholarship Mr. Bander AlKhodairy

CORE FACILITY ACTIVITIES

The CSCF User Support team is dedicated to support all computer users to gain maximum productivity and efficiency from computer for research purpose.

During the year 2011 CSCF setup new PCs, laptops, workstation, printers, servers and other major computer peripherals. The CSCF has successfully installed and configured three servers which will be used by Registry Core facility to help them to develop state of art registry applications.

Additional disk space installed for the following servers:

- Al-Biruni (Production server)–400 GB, IBNKHALDUN (File Server)–900 GB.
- Al-Kindi (File Server)–900 GB, Al-Haitham (CDU Server)–400 GB.

Upgrading network for 2 workstation from (100 Mbps) to (1 Gbps) to maintain a fast data transmission which will be utilized by Genetics Department.

Helped Al-Saif Company to install servers for Tissue Bank unit at KFNCCC&R.

The Computer Services Core Facility (CSCF) setup and configured:

- 78 new PCs and distributed to assigned departments
- 6 new laptops
- 10 scanners
- 5 fax machines
- 20 printers

Preventative Maintenance

CSCF successfully carried out the preventative maintenance (PM) in the BESC department. The preventative maintenance is carried out on quarterly basis which consists of tasks that would boost the performance of the machines, stabilize platforms, and increase the productivity and efficiency and will also reduce the support costs.

These tasks are related but not limited to:

1. Operating systems update
2. Disk defragmentation
3. Software updates
4. Service packs for windows and MS Office
5. Cleaning internet browser temporary internet and offline files
6. Updates of the anti-virus software

Helpdesk

At the Research Centre, CSCF serves as the computer users' support hub, effectively a catch-all helpdesk. Requests for assistance are received electronically and farmed out to the technical staff for resolution.

Configuration and Distribution

New equipment for the Research Centre, such as computers, monitors, printers, and other peripherals, are received at CSCF. Computers are then configured according to predetermined standards, appropriate software packages installed, and then units are subsequently delivered to respective departments.

Pre-procurement Analyses

Work involved in determining system configuration for new computers, be these user PCs, instrument PCs, or additional servers, is a CSCF concern. Further, CSCF makes sourcing recommendations that cover

vendor comparisons, price-performance analyses, and post-sale support assessments.

KFNCCC&R Support
CSCF's operations reach beyond the main facility of the Research Centre. The King Fahad National Centre for Children's Cancer & Research (KFNCCC&R) hosts three offsite laboratories of the Research Centre—the SDL-Saudi Diagnostics Laboratory, the Human Cancer Genomics Laboratory, and the Laboratory Animal Facility of the Department of Comparative Medicine. These laboratories are visited by CSCF staff on a regular basis and receive the same degree of support as those located at the main facility.

The Central Data Unit of Pediatric Hematology-Oncology at the KFNCCC&R, having originated from a collaborative effort between PHO and BESC, is also covered by CSCF support.

ITA and CSCF
CSCF maintains a close functional relationship with Information Technology Affairs, the Hospital's IT management unit. CSCF liaises with ITA on a regular basis, mostly on matters pertaining to deliveries of computer hardware, utilization of the network infrastructure, and management of RC users' network accounts.

Core Facility activities breakdown by department:
CSCF has setup and configured PCs, Laptops, Workstations, Printers, and Scanners for the following departments:

- Biological and Medical Research
- Biomedical Physics
- Biostatistics, Epidemiology and Scientific Computing
- Comparative Medicine
- Cyclotron and Radiopharmaceuticals
- Genetics
- KFNCCC&R
- Oncology Data Unit Department of Oncology
- RC Administration

Following is the summary of the calls per department logged by CSCF during the year 2011:

Department	No. of Logged Calls
BESC	530
BMP	265
BMR	450
CCR	159
CMD	184
CPPEO	139
C&R	173
Genetics	152
ORA	125
RC-Admin	95
Stem Cell Therapy	200
T&E	112
KFNCCC-Research (CDU)	90
KFNCCC-Research (SDL)	100
KFNCCC-Research (HCGL)	130

BIOMEDICAL PHYSICS

BIOMEDICAL PHYSICS

CHAIRMAN
Belal Moftah, PhD, FCCPM

DEPUTY CHAIRMAN
Ghazi Alsbeih, MD, PhD

ADMINISTRATIVE STAFF
Dena Al-Assailan
Irene Banguilan, BSc *(RC Grant Employee)*
Marilou Co, BSc *(RC Grant Employee)*
Mildred San Pedro, BSc *(RC Grant Employee)*
Josephine Veridiano, BSc

The 2011 annual report of the Biomedical Physics Department highlights the remarkable achievements that we have made over the past year which were attributed largely to the services we provide for clinical departments in support of quality patient care. The expertise of our staff members has been instrumental in the success of radiation therapy patient treatments and diagnostic imaging procedures through the introduction and implementation of state-of-the-art techniques. We have continued to maintain a radiation-safe environment for all KFSH&RC personnel, patients and the general public through our radiation safety programs. In addition, the department has been actively involved in clinical and basic research, continuing education, and in various business and income producing activities.

The major achievements of the Department in 2011 are briefly summarized in the following:

- Provision of physics support services and treatment planning to cancer patients undergoing radiotherapy treatment. Our Radiation Physics team, which constitutes medical physicists and medical dosimetrists, dealt with about 1900 cancer patients in 2011. A total of approximately 3,405 clinical dosimetry and treatment planning procedures were performed for patients.
- Accreditation of our radiation physics procedures, machine output and the American RTOG protocols by the Radiological Physics Center of MD Anderson Cancer Center.
- Management of a regional pilot residency the "IAEA ARASIA Residency Program for Medical Physicists in Radiation Oncology" at KFSH&RC in collaboration with the International Atomic Energy Agency.
- Development and Recognition of staff expertise through passing of internationally recognized board certifications: One staff was board certified by the Canadian College of Physicists in Medicine, and three by the American Medical Dosimetry Certification.
- Hosting of the Regional Training Course on Radiotherapy Techniques with Emphasis on Imaging and Treatment Planning on 09–13 October 2011, the Course and Workshop on QC of Gamma Camera SPECT/CT System, on 09–12 May 2011, and the 6th Saudi Medical Physics Conference, on 04–06 December 2011.
- Training of 7 International Atomic Energy Agency (IAEA) Fellows in Radiation Physics Section and 3 in Imaging Physics Section of the Department.
- Training of 8 undergraduate and graduate students from different universities within the Kingdom.
- Management as Principal Investigator of 6 approved research projects funded by King Abdulaziz City for Science and Technology.
- Participation of our Secondary Standard Dosimetry Laboratory in the IAEA annual postal dose audit for radiotherapy energy level of calibration where it obtained a very satisfactory result. A total of 1108 radiation measuring instruments were calibrated by our SSDL during this reporting period.
- Provision of Thermoluminescent Dosimetry (TLD) radiation monitoring services within and outside KFSH&RC. A total of 18,196 personnel were monitored during this year.
- Sterilization of bones in our Gamma Irradiation Facility for the Bone Bank at KFSH&RC.
- Renewal of ISO certification for the Gamma Irradiation Facility.
- Establishment of the 1st Biological Dosimetry Laboratory in the Kingdom.
- The 1st to publish on the prevalence and genotypes' distribution of human papilloma virus infection in Saudi cervical cancer patients and advise consequently on HPV vaccine.
- Publications of manuscripts in international scientific journals and book chapter in an open access book.
- Publications of 6 news in Arabic public media highlighting research findings, awards and activities of staff of the Biomedical Physics Department.
- Collaboration with 7 national and 4 international institutions as well as regulatory agencies on service, research and education levels.
- Renewal of the Radiation Safety Office licenses from KACST to import radioactive material, as well as for scientific research and Nuclear Medicine.

Details of activities of the following sections, units and core facilities of the Biomedical Physics Department for the year 2011 are shown in separate reports:

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

RESEARCH PROJECTS

We have six approved research projects funded by King Abdulaziz City for Science and Technology, as follows:

1. KACST Grant Project #10–BIO960–20: Development of Novel 3D Gel Dosimetry System for Radiation Oncology Treatment Verification. PI: Belal Moftah, PhD, FCCPM
2. KACST Grant Project #AT-25–85: "Establishment of a Monte Carlo-based Clinical Dosimetry Center in Saudi Arabia. (Project # 2060 026)". PI: Belal Moftah, PhD, FCCPM
3. KACST Grant Project #10–BIO1428–20: "Intra-Operative Proton Radiotherapy (IOpRT). PI: Belal Moftah, PhD, FCCPM. PI: Belal Moftah, PhD, FCCPM
4. KACST Grant Project #10–MED989–20: Functional Imaging of Infants and Toddlers with Autism. PI: Rami Niazy, PhD
5. KACST Grant Project #09–MED 749–20: Developing Biological Dosimeters for the Assessment of Radiation Overexposure in Nuclear Accidents. PI: Ghazi Alsbeih, MD, PhD
6. KACST Grant Project #10–BIO1429–20): Assessing the Genotypes' Distribution of Genetic Polymorphic Variations and their Impact on the Risk of Radiation Exposure in Saudi Individuals. PI: Ghazi Alsbeih, MD, PhD

FUTURE RESEARCH DIRECTION

The Department has continued to encourage its staff to have a protected time to do research for projects that are of relevance to improving the quality of clinical service and research program at KFSH&RC.

PUBLICATIONS

- Omar Chibani, Belal Moftah and Charlie Ma, "On Monte Carlo modeling of megavoltage photon beams: A revisited study on the sensitivity of beam parameters". *Medical Physics* 38, 188 (2011)
- Ahmad Nobah; Belal Moftah; Nada Tomic; Slobodan Devic, Influence of electron density spatial distribution and X-ray beam quality during CT simulation on dose calculation accuracy. *Journal of applied clinical medical physics / American College of Medical Physics* 2011;12(3):3432.
- Omar Chibani and Charlie C-M. Ma., "Photonuclear Dose From High Energy Medical Linear Accelerators". Presented at American Nuclear Society Winter Meeting, November 2011 and Published in *Transactions of the American Nuclear Society* (2011).
- Ghazi Alsbeih. Chapter title: MRE11A Gene Mutations Responsible for the Rare Ataxia Telangiectasia-Like Disorder. Book title: Human Genetic Diseases. ISBN 978–953–308–96–7. Book edited by: Djana Plaseska-Karanfilska, MD, PhD, *InTech Open Access Publisher*. September 2011. Chapter 4:79–90.
- Khaled S. Al-Hadyan, Najla M. Al-Harbi, Sara S. Al-Qahtani, Ghazi A. Alsbeih. Involvement of single nucleotide polymorphisms in predisposition to head and neck cancer in Saudi Arabia. Genetic Testing and Molecular Biomarkers. 2012 Feb;16(2):95–101. *Epub* 2011 Aug 30. PMID: 21877955.
- Ghazi Alsbeih, Raef Ahmed, Najla Al-Harbi, L. Aubrey Venturina, Asma Tulbah, and Khalid Balaraj. Prevalence and genotypes' distribution of human papilloma virus in invasive cervical cancer in Saudi Arabia. *Gynecologic Oncology*, 2011 Jun 1;121(3):522–6. *Epub* 2011 Feb 24, PMID: 21353296.
- Ahmed A. Basfar, Khalid A. Rabaeh, Akram A. Moussa, Rashed I. Msalam. Dosimetry characterization of nitro-blue tetrazolium polyvinyl butyral films for radiation processing. *Radiation Physics and Chemistry*, Volume 80, Issue 6, June 2011, Pages 763–766.
- Sayed MG, Al-Shehri MY and Elwood TW. Allied Health Professions Education in Saudi Arabia: Progress and Limitations. *Saudi Journal of Higher Education*. 6(2):6–33, December 2011.
- H. I. Al-Mohammed. Measuring patient's skin dose during total skin electron therapy using MOSFET. *Biomedi Res* 2011; 22 (1): 9–14.

- H. I. Al-Mohammed. The efficiency of using audio prompting method to regulate the patient's breathing during radiation therapy treatment of NSCLC. *IJMS*, 2011; 3(1): 1–6.
- Huda Ibrahim Al-Mohammed. Evaluation of clinical use of OneDos™ metal oxide semiconductor field-effect transistor detectors compared to thermoluminescent dosimeters to measure skin dose for adult patients with acute lymphoblastic leukemia. *N A J Med Sci*. 2011, 3(8). 11–17.
- H. I. Al-Mohammed. Patient Specification Quality Assurance for Glioblastoma Multiforme Brain Tumors Treated with Intensity Modulated Radiation Therapy. *I J Medi Sci*; 2011; 8(6):461–466.
- H. I. Al-Mohammed and F. H. Mayhoub Patient-specific quality assurance for the treatment of intensity modality radiation therapy of nasopharyngeal carcinoma. *JCREO*, 2011; 3(2)6–17.

Radiation Biology Section (Biomedical Physics Research)

HEAD
Ghazi Alsbeih, PhD

MEMBERS
Najla Al-Harbi, BSc
Muneera Al-Buhairi, BSc
Khaled Al-Hadyan, BSc *(on study leave)*
Sarah Al-Qahtani, BSc *(RC Grant Employee)*
Elen Dela Cueva *(RC Grant Employee–until April 2011)*
Lorcel Aubrey Venturina, BSc *(RC Grant Employee)*

The discipline of radiation biology provides the biological basis of the many uses of radiation in medical and allied health professions. It is devoted to study the interaction between radiation and living materials and organisms. The aim is to better understand and master this tool in health and medicine and therefore, to improve its beneficial effects and avoid its hazardous potential.

RESEARCH PROJECTS

PROJECT TITLE: **Cervix carcinoma: HPV infection, genetic predisposition and biomarkers of response to chemo-radiation therapy**

KACST ARP # 12–27. ORA # 2060 029.

INVESTIGATORS: *Ghazi Alsbeih, Khaled Balaraj, Medhat El-Sebai, Belal Moftah*

PROJECT DESCRIPTION: Cervical cancer is the second most common cancer among women worldwide and persistent infection with human papillomavirus (HPV) has been identified as a main risk factor for its development. The oncoproteins E6 and E7 of high-risk HPVs can bind to and degrade the tumor suppressor gene (TSG) products p53 and pRb that interact with the cell cycle checkpoint causing host cell over-proliferation and genome instability. However, since only a subset of HPV infected patients will eventually develop cervical cancer, additional factors are needed for carcinogenesis. It has been suggested that Muslim women have lower incidences of cervical cancer and/or HPV infection raising the question of important environmental, cultural and genetic differences with western countries. Cervical cancer ranks number 8 in Saudi Arabian women forming 3.4% of newly diagnosed cancer cases; however, it is frequently diagnosed at advanced stages requiring chemo-radiation therapy. In developed countries, the widespread use of Papanicolaou (Pap) smear has dramatically reduced cervical cancer incidence and mortality. HPV DNA testing is expected to improve the outcome of screening programs and the advent of vaccines against HPV infection represents promising approach for the future prevention of cervical cancer. Studies on cervical cancer in Saudi Arabia are lacking. This project proposes to investigate the relationships between HPV infection, HPV genotype, cellular radiosensitivity, the presence of certain single nucleotide polymorphisms (p21 31 C>A, p53 72 G>C, A™ 1853 G>A and 1853 A>T, MDM2 309 promoter T>G, MDM2 110 A>G, DNA Ligase IV 591 A>G, XRCC1 399 G>A, XRCC3 241 C>T and TGFβ1 10 T>C) and the risk, severity and response to chemo-radiotherapy of cervical cancer patients treated at KFSH&RC. One hundred women with locally advanced cervical cancer treated with curative radiotherapy will be enrolled. Cervix tumor and punch skin biopsies will be taken from each patient and will be analyzed. Results should allow better understanding of the specificity, if any, of cervical cancer in our community and paves the way for the implementation of screening and prevention programs to reduce the high mortality related to delayed diagnosis.

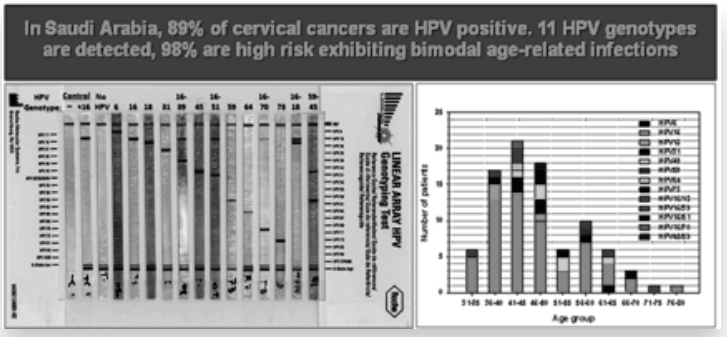
PROGRESS: Results on 100 cervical cancer patients have been published. The abstract is:

OBJECTIVE: Data concerning HPV infection in cervical cancer are globally lacking in Saudi Arabia. Therefore, the aim of this study was to assess HPV prevalence and genotypes' distribution in invasive cervical cancer in our patients to provide baseline information for screening and prevention.

METHODS: The study included 100 paraffin-embedded cervical tumors. HPV genotyping was performed using the Linear Array kit (Roche Diagnostic) that enables the concomitant detection of 37 mucosal HPVs including 13 most common high risk viruses.

RESULTS: Eighty-nine specimens were HPV-positive. Eleven different HPV genotypes were detected, 8 high risk (16, 18, 31, 39, 45, 51, 59, 73) and 3 low risk (6, 64, 70). Ten patients had double infections involving mainly HPV-16 and 18. The most common genotypes were: 16 (65.2%), 31 (7.9%), 45 (6.7%), 18 (3.4%), and 73 (2.3%). However, by considering double infections, HPV-18 became the 2nd most common genotype (10.1%). The patients' median age was significantly lower ($P = 0.028$) in HPV-16/18 infected group compared to other genotypes (44, range 32 to 76 vs. 49, range 38 to 67).

CONCLUSIONS: Eighty-nine percent of cervical cancers in Saudi Arabia were associated with HPV infection, 78.7% (70/89) of HPV positive tumors were infected with HPV-16/18, which caused the cancer to appear 5 years earlier than the combined HPV-negative and other HPV genotypes ($P = 0.013$).



PROJECT TITLE: **DNA double strand breaks as a mechanism for radiosensitization induced by gemcitabine in p53 wild-type and mutant breast cancer cell strains**

ORA # 2090 031

INVESTIGATORS: *G. Alsbeih (PhD), F. Abu Tarbush (PhD), S. Salem (MSc student)*

PROJECT DESCRIPTION: Breast cancer is the most common cancer in women accounting for one third of all malignancies. It is classified into 4 clinical stages. Metastatic breast cancer (Stage IV) is characterized by the spread of distant metastases to other parts of the body, such as the bones, brain, lung or liver (Chew et al., 2009). Treatments are primarily palliative. Toxicity and adverse effects will therefore play an important role in treatment decisions, with quality of life being a key consideration (Yardly et al., 2008). Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. The drug disrupts cell replication by incorporating itself directly into the DNA and radiosensitizes the tumor cells. However, its mechanism of action is still not well chracterized. The mutational status of p53 seems to play a role but it is not clear if this related to cell cycle control or DNA double-strand breaks repair. Balancing the toxicities of therapy with the cancer-controlling benefits in individual patients, and the development of effective and well-tolerated regimens requires better understanding of gemcitabine's mode of action. The overall significance comes within the framework of individualizing cancer treatment. When achieved, this will lead to custom-design cancer treatment to each individual patient's radiosensitivity. This is expected to improve the therapeutic results by avoiding severe complications and increasing tumor control probability. Clinical trials are under way with dFdCyd and radiotherapy in several different malignancies. Additional studies to understand the critical events required for radiosensitization with dFdCyd may lead to improvements in the administration of this clinically promising therapy.

To better understand the mechanism of action of gemcitabine, we propose to examine the role of DNA dsbs on its ability to produce radiosensitization in wild-type (MCF7) and mutant (MDA-MB-231) p53 breast cancer cell lines. In addition, the normal mammary cell line MCF-12 will be used to study the effect on normal tissue. Radiosensitivity will be measured by the clonogenic survival assays. DNA double-strand breaks will be using the pulsed-field gel electrophoresis (PFGE) technique that measures the total dsbs induced, the rate of repair and the residual dsbs unrepaired.

PROGRESS: Gemcitabine (2',2'-difluoro-2'-deoxycytidine; dFdCyd) is reported in many studies as radiosensitizer. It is one of the anti-metabolites drugs that target DNA replication. We evaluated dFdCyd cytotoxicity in two human breast cancer cell lines MCF-7 (wild-type p53) and MDA-MB-231 (mutant-type p53) and MCF-12 (normal mammary epithelial cell line) to evaluate the effect on normal tissue. The results demonstrated that MDA-MB-231 cells were

the most sensitive to the cytotoxicity of dFdCyd (IC50 5nM) then MCF-7 (IC50 10nM), whereas MCF-12 cells were the most resistant to the cytotoxicity of dFdCyd (IC50 70nM). The results pointed out that MCF-12 and MCF-7 cell lines did not show any radiosensitization to dFdCyd, even at equimolar concentration (10nM) or at IC50 concentration of each cell line, whereas the MDA-MB-231 cells showed increased radioresistant to dFdCyd at equimolar concentration (p=0.002) and at IC50 concentration (p<0.001). The DNA double strand breaks (DSBs) repair results in the current study was agreed well with the results of cell survival. The results showed that dFdCyd neither increases DNA DSBs nor decreases the rate of their repair in MCF-12 and MCF-7 cells, while the same treatment in MDA-MB-231 cells line led to decrease the rate of DSBs or increase the rate of DNA repair (p=0.034). Therefore the dFdCyd is a cytotoxic agent, especially in the cancer cells even it has wild-type or mutated p53 protein. Lack of gemcitabine efficacy as radiosensitizer in all cell lines used in the current study, and this efficacy vary depending on the cell line used.

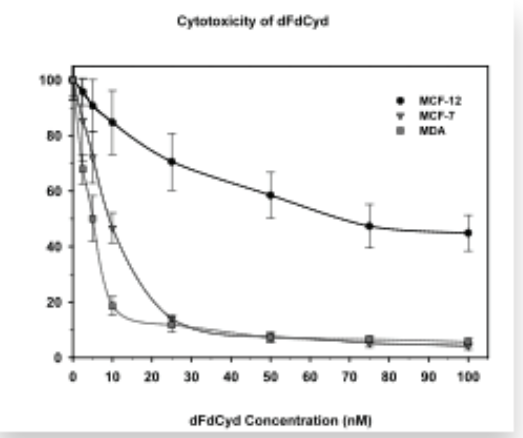


Figure. Cytotoxicity of dFdCyd in human breast cancer cells and normal mammary epithelial cells. MCF-7 (▼), MDA (■) and MCF-12 (●) cells were incubated with dFdCyd for 48 h and assayed for clonogenic survival.

Cell Strain	Treatment	α	β	SF2	Db (MID)	RER (MID R/MID R+dFdCyd)
MCF-12	R	0.333	0.060	0.40	1.934	
	R+G 10 nM	0.236	0.068	0.47	2.173	0.890
	R+G 70 nM	0.052	0.098	0.61	2.581	0.749
MCF-7	R	0.423	0.025	0.39	1.960	
	R+G 10 nM	0.409	0.034	0.38	1.914	1.024
MDA	R	0.619	0.033	0.25	1.421	
	R+G 5 nM	0.509	0.000	0.33	1.967	0.722
	R+G 10 nM	0.366	0.004	0.47	2.595	0.548

Table: Survival data of human breast cancer cells and normal mammary epithelial cells. MCF-12, MCF-7 and MDA-MB-231cells were treated with the indicated doses of dFdCyd for 4 hours. Values represent a mean ± SE for at least three experiments.

FUTURE RESEARCH DIRECTION

We are expanding our work on biological dosimetry in Saudi Arabia.

PUBLICATIONS

- Ghazi Alsbeih, Raef Ahmed, Najla Al-Harbi, L. Aubrey Venturina, Asma Tulbah, and Khalid Balaraj. Prevalence and genotypes' distribution of human papilloma virus in invasive cervical cancer in Saudi Arabia. *Gynecologic Oncology*, 2011 Jun 1;121(3):522–6. Epub 2011 Feb 24, PMID: 21353296.
- Ghazi Alsbeih. Chapter title: MRE11A Gene Mutations Responsible for the Rare Ataxia Telangiectasia-Like Disorder. Book title: Human Genetic Diseases. ISBN 978–953–308–96–7. Book edited by: Djana Plaseska-Karanfilska, MD, PhD, *InTech Open Access Publisher*. September 2011. Chapter 4:79–90.

ABSTRACTS/CONGRESS PROCEEDINGS:

- Ghazi Alsbeih, Najla Al-Harbi, Khaled Al-Hadyan, Muneera Al-Behairi. Radiation sensitivity and frequency of MRE11 gene mutations responsible for the Ataxia Telangiectasia-Like Disorder (ATLD) in Saudi Arabia. Poster Presentation. 14th International Congress of Radiation Research and the Annual Meeting of the Radiation Research Society, Warsaw, Poland, August 28–September 1, 2011.
- Ghazi Alsbeih. Ataxia telangiectasia-like disorder (ATLD) in Saudi Arabia: Mre11 gene mutations, frequency and cellular radiosensitivity. Poster. Human Genome Meeting 2011, Dubai, United Arab Emirates, 14–17 March 2011.
- Khaled Al-Hadyan, Najla Al-Harbi, Sara Al-Qahtani, L. Aubrey Venturina, Muneera Al-Buhairi, Sameer Salem, Raef Ahmed, Khalid Balaraj, Ghazi Alsbeih. Involvement of TP53 G/C codon 72 polymorphism in predisposition to cervical cancer in Saudi patients. Human Genome Meeting 2011, Dubai, United Arab Emirates, 14–17 March 2011.

Clinical Dosimetry and Treatment Planning Unit

HEAD
Belal Moftah, PhD, FCCPM

MEMBERS
Baderaldeen Al Tazi, BSc *(RC Grant Employee until Feb. 2011)*
Manal Awidah, BSc *(Grant Employee)*
Osama Hassad, MSc, CMD
Ghadeer Nazer, BSc, CMD
Wedyan Safar, BSc, CMD
Ericka Venturina, BSc, CMD *(RC Grant Employee)*
Paula Yates, RT(T), CMD

The year 2011 was an active year within the dosimetry unit as it was for the Radiation Physics Section as a whole. We had a large focus on training others outside of our Unit this year, from both within and outside KFSH&RC.

For 2012 our plan remains to introduce CT planning for almost all patients regardless of their treatment intent (radical or palliative). We will also be implementing new linear accelerators which will require our current planning system (Varian's Eclipse) to be upgraded with additional training to coincide with that. Also we expect training, and therefore, more utilization of the additional systems we have in place, such as Velocity and Pinnacle.

One of the key aims for 2012 is to improve our staffing as we have been under-staffed for over two years now.

ACTIVITIES	YEAR 2011
Monitor Unit (MU) Calculation/2–Dimensional Contour	306
Total Body Irradiation (TBI) Calculation	46
3–Dimensional CT Treatment Planning	1352
Stereotactic Radiosurgery/Radiotherapy (BrainLab)	0
Electron Cut-out Measurement	125
Intensity Modulated Radiation Therapy (IMRT)	152
RapidArc	140
Tomotherapy	171
Cyberknife	116
TLD Dosimetry	50
Total Skin Electron Treatment (TSET)	0
High Dose-Rate (HDR) Brachytherapy	34
Low Dose-Rate (LDR) Brachytherapy	0
Clinical Consultation	50
Free-Hand Set-Up (FHSU)	6
TOTAL PROCEDURES	**2548**
PATIENTS	**1218**
MANHOURS	**10400***

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

TRAINING AND EDUCATION ACTIVITIES

The main event for our staff, as lecturers and instructors, was the IAEA Regional Training Course on Radiotherapy Techniques with Emphasis on Imaging and Treatment Planning, held at KFSH&RC in October 2011.

We continue to provide training in clinical dosimetry and treatment planning to physics undergraduate and graduate students from different universities within the Kingdom and also to individuals from ARASIA member-countries (we had four physicists from Yemen come through the Unit for dosimetry knowledge in 2011). 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. Three of our Senior Dosimetrists (Ms Nazer, Ms Safar and Ms Yates) were appointed as Supervisors for the dosimetry rotation within the ARASIA Residency for Medical Physicists in Radiation Oncology Program, mentoring two physics residents each during the year.

The biggest achievement of our Unit was three of our full-time Dosimetrists (Mr Hassad, Ms Nazer and Ms Venturina) sitting and passing their Certified Medical Dosimetry examinations from the American Medical Dosimetry Certification Board—the only internationally recognized medical dosimetry certification. This now means that five out of our six full-time dosimetrists are Certified Medical Dosimetrists (CMD). This figure is well above the average for any North American dosimetry unit and something that we are very proud of.

We are expecting all our Dosimetry Unit staff to be busy as instructors in the build up to and during the International Conference on Radiation Medicine 2012. This will be the third such conference to take place at KFSH&RC, on February 27–March 1 2012.

STAFFING

Due to our continuing staff shortage, made worse by senior staff resignations at the end of 2009 and non-recruitment into these vacant positions through-out 2010 and 2011, 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 2012 to enable increased participation in research activities and production of scientific papers based around our knowledge of advanced radiation treatment modalities. Also we would like to upgrade our current staff dosimetrists, who have been acting Senior Medical Dosimetrists for many years, into actual senior positions/grades.

At the least we would like to recruit a compatible Chief Medical Dosimetrist to lead the Unit in a full-time capacity and award our two hard working Grant Employees (Ms Awidah and Ms Venturina) with permanent positions.

Gamma Irradiation Facility

HEAD
Akram Al-Moussa, MSc

MEMBERS
Saad Bin-Jamaan, BSc
Edilberto Delos Reyes

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

STAFF OF THE FACILITY

- One Engineer, Head of the facility, dosimeterist.
- One operator, (50 % part of his time running the Biomedical department business office).
- One Technician (Retired and we extend his contract with exception).

CORE SERVICE ACTIVITIES

The activities of the Gamma Irradiation Facility are:

- Continued to provide sterilization for hospital needs (Bone bank, Cyclotron kits and supplies of ART laboratory and biomedical research section).
- Provided gamma irradiation services for Master Degree students from King Saud University, with doing the necessary dosimetry for their samples. (Currently we have three MSc students Dr. Abeer Abdulkarim Al Mahdi, Dr. Hanan Abdulghafor Balto from Dental College, and Ms. Sita Mufleh Al Harithi, from Pharmaceutical Sciences College; helping them in doing their research). Upon initiating the business office in biomedical physics department we are sterilizing for University students with fee.
- 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 are 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).
- Research project with KACST, National Biotechnology on the 3D gel dosimetry for radiation therapy of cancer patients, trying to modify a new gel composition dosimeter is going very well and the results are promising.
- 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 Facility can doubles its income generating opportunities many times through sterilization of medical products/ materials if KFSH&RC develop the facility to follow the latest technology and stay in competition with new very fast irradiators. New product can be manufactured here in the KFSH&RC if we achieve the new development, which is the hydrogel wound dressing; a special composition for the hydrogel was developed in GIF laboratory.

The Radioactive source installed in 2003 is 9 years old and has one and half of its half life the source activity decreased from 300 kCi of Cobalt-60 to 92 kCi which affect the time of irradiation. One of the suggestions is to transfer into electron beam technology which is faster and cut the decay expenses of the gamma source.

- 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 sterilize with Gamma radiation. The new cyclotron commercial kits manufacturing project that suppose to start as soon as the new building finish, will depends mainly on Gamma sterilization as part of line of production. All dosimetry studies were done and ready to sterilize 200 kits/week. Again the Gamma is the only technique for sterilizing those kits.
- The Facility has one of the best dosimetry laboratories in the region with annual intercomparison program with National laboratory of RISO, DENMARK. We calibrated the Gamma Cells in KACST and they request our help to do this calibration from time to time.

Health Physics

HEAD
Fareed Mahyoub, MSc, MIPEM

MEMBERS
Celestino S. Lagarde, BSc
Ibrahim Al-Gain, BSc
Noura Al-Mulhem, BSc *(RC Grant)*
Arwa Helmi, BSc *(RC Grant)*

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

HEALTH PHYSICS ACTIVITIES

The table below summarizes the accomplishments made by the Health Physics Section for year 2010 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	3903
No. of Personnel Radiation Monitoring performed	18,196
Patients surveyed for radiation level	242
Patients rooms surveyed for radiation level	238
Patients rooms decontaminated	242
Leak test for sealed sources and radiation producing equipment	168
TLD badges irradiated for quality control of TLD readers of outside facilities	111
Consultative advice provided	310
Training courses & educational lectures provided	12

Imaging Physics Section

HEAD
M. Gary Sayed, PhD, FACNM

MEMBERS
Ibrahim Al-Anazi, MSc, ABHP
Refaat Y. Al-Mazrou, MSc, MIPEM
Adnan Z. Al-Watban, PhD
Omer Demirkaya, PhD, DABSNM
Nabil I'Qilan, MSc

As a clinical science support endeavor, most of imaging physics section's activities are focused on providing 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), ultrasound, positron emission tomography (PET), PET/CT, nuclear medicine (including SPECT/CT) and magnetic resonance imaging (MRI).

Most of the clinical services provided fall under the broad category of imaging equipment acquisition, implementation and proper operation. The process starts with 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 technology, assisting with clinical trials, and performing patient radiation exposure/image quality optimizations. Section staff is also involved in numerous continuing education training programs and in regional associations/local societies to promote the discipline of diagnostic radiologic and nuclear medicine physics.

RESEARCH PROJECTS

PROJECT TITLE: **Lesion Quantification in Whole Body Images of Positron Emission Tomography (PET)**

INVESTIGATOR: *O. Demirkaya*

PROJECT DESCRIPTION: In PET, identification of lesion boundaries in general is not a trivial problem due to the limited image resolution and image inhomogeneity. Manual methods discourage physicians from taking advantage of the inherently quantitative data and help them opt for qualitative means in their diagnosis and assessment of the patient response to therapy. Recently, the automated identification of the lesion boundaries has become a critical issue in the use of PET in radiation treatment planning. In this study, we intend to develop lesion quantification techniques to analyze/quantify lesions in the whole-body images of PET. We envisage that automated or semi-automated quantification methods will help physicians facilitate their diagnosis and enable them to extract maximum or mean SUV values from a lesion volume. It may also allow them to track small changes in lesion characteristics, which may be difficult to observe visually. Since we intend to incorporate the PET images into the radiation treatment planning system, this effort will help to the PET physicians to make a better judgment about the tumor boundaries.

PROGRESS: We have developed a fully automated method that identifies tumor lesions in the whole body volume. We also developed a lesion analysis method that computes the tumor and background characteristics. We compared it against a widely used method. Ongoing research investigates the lesion detectability performance of the method on a large number of data set. The results of this research have been presented in international conferences.

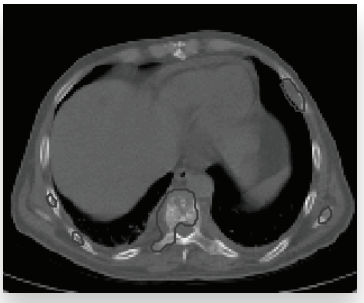
PROJECT TITLE: **A non-invasive and sensitive molecular blood assay to evaluate treatment response /relapse in women with breast cancer**

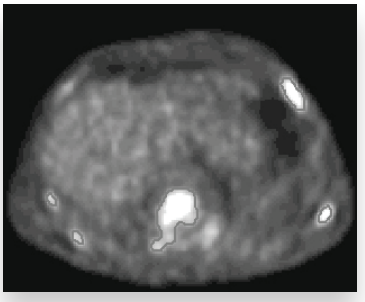
CO-INVESTIGATOR: *O. Demirkaya*

I am a co-investigator in this project that is recently approved by KACST and RAC (# 2110 20). My role will be correlating the molecular blood assay results with the PET results.

FUTURE RESEARCH DIRECTION

Two main 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 verses just CT or MRI) thus minimizing the time of diagnosis and reducing radiation exposure to patients. The other main project is slated to be launched in the summer of 2011 and involves the in-vitro dosimetric assessment of targeted radionuclidic therapy applications of new beta-radiation emitters such as Lu-177.





Molecular and Functional Imaging

HEAD
M. Gary Sayed, PhD, FACNM

MEMBERS
Rami Niazy, PhD

Presently in its third year of existence, the Molecular and Functional Imaging (MFI) group has pursed both intramural and extramural funding in congruence with its strategic plan. To that end, four grant applications were prepared this year and submitted for to various funding agencies. One of those applications has been funded by the KACST under the biotechnology initiative. The MFI group is in the process of implementing the functional imaging research activity funded by KACST by requesting space and infrastructure support. The project PI, Dr. Rami Niazy, has recently hired a postdoctoral fellow to initiate the proposed experimental work. The MFI group is still waiting for outcomes of intramural funding requests.

Radiation Physics Section

HEAD
Belal Moftah, PhD, FCCPM

MEMBERS
Aldosary, Ghada, BSc, *(RC Grant Employee until June 2011)*
Al-Kafi, Mohd Abdullah, MSc
Al-Mohammed, Huda, PhD
Al-Najjar, Waleed, PhD, DABR *(Adjunct Appointment)*
Ashmeg, Sarah, BSc *(On study leave)*
Chibani, Omar, PhD
El-Kaissi, Tarek, PhD, DABR *(Resignation: July 2011)*
Hassan, Zeinab, PhD
Hussain, Mohamed Abrar, PhD, DABR
Mahyoub, Fareed, MSc, MIPEM
Mwidu, Umar, MSc
Nobah, Ahmed, MSc
Santos, Rikka Maureen, MSc *(RC Grant Employee)*
Shehadah, Mamoun, MSc
Yan, Xiang Sheng, MSc

The radiation physics section of the biomedical physics Department is largely engaged in its clinical physics and quality assurance services for cancer patients receiving radiation therapy. Our Radiation Physics team, which constitutes medical physicists and medical dosimetrists, dealt with about 1900 cancer patients in 2011. A total of approximately 3,405 clinical dosimetry and treatment planning procedures were performed for patients using the highly sophisticated state-of-the-art radiotherapy equipment at KFSH&RC. Our Radiation Physics team played a vital role in the effective and safe clinical utilization of the three major radiotherapy treatment modalities namely, TomoTherapy, CyberKnife, and RapidArc. The radiation physics team also effectively modified the brachytherapy treatment from 2D to 3D. Last year, approximately 85 physics procedures were completed. 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 is a unit under the Radiation Physics Section. It is charged with conducting radiation treatment plans and dosimetric calculations for a wide variety of malignant cancers and benign diseases.

One major undertaking of the Section is the introduction of the medical physics residency training program and development of staff expertise by passing internationally recognized board certifications: One staff was board certified by the Canadian College of Physicists in Medicine, and three by the American Medical Dosimetry Certification in 2011.

During this reporting year, our staff members were also widely in the (a) training of 7 International Atomic Energy Agency (IAEA) Fellows, (b) hosting of the IAEA Regional Training Course on Radiotherapy Techniques with Emphasis on Imaging and Treatment Planning hosted at KFSH&RC in October 2011, and (c) preparation for the upcoming ICRM2012.

RESEARCH PROJECTS

PROJECT TITLE: **Establishment of a Monte Carlo-based Clinical Dosimetry Center in Saudi Arabia**

Project # 2060 026

PRINCIPAL INVESTIGATOR: *Belal Moftah, PhD, FCCPM*

PROJECT DESCRIPTION: The project will offer the capability of providing accurate clinical Monte Carlo treatment plans required for cancer patients to institutions in the Kingdom and accurate modeling of radiation treatment units in the country.

PROGRESS: During last year, an abstract was presented at the 52nd Annual Meeting of the American Association of Physicists in Medicine (AAPM) in Philadelphia, USA, July 18–23, 2010. Furthermore, a peer-reviewed manuscript was published in the prestigious American Medical Physics Journal. (KACST Project No. AT-25-85. Approved funding: SR 652,000).

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

PRINCIPAL INVESTIGATOR: *Belal Moftah, PhD, FCCPM*

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: A grant proposal was submitted to the KACST Advanced and Strategic Technologies program and approved for funding (Budget approved: SR 2.0 Million). The first objective was mostly achieved by receiving, installing and running the laser optical CT (Octopus). The training on the optical CT was already done and more experience with the system is being gathered. Research work is continuing.

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

PRINCIPAL INVESTIGATOR: *Belal Moftah, PhD, FCCPM*

PROGRESS: A grant proposal submitted to KACST's Advanced and Strategic Technologies program of the National Comprehensive Plan for Science and Technology. (KACST Grant Project # #11-BIO1428-20. Approved funding: SR 2.0 million).

PROJECT TITLE: **Developing Biological Dosimeters for the Assessment of Radiation Overexposure in Nuclear Accidents"**

CO-PRINCIPAL INVESTIGATOR: *Belal Moftah, PhD, FCCPM*

PROJECT DESCRIPTION: KACST Advanced and Strategic Technologies program of the National Comprehensive Plan for Science and Technology. (Project # 08-MED749-20, 24 months. Budget Approved: SR 2.0 million).

FUTURE CLINICAL RESEARCH DIRECTION

PROJECT TITLE: **Comprehensive Radiotherapy Treatment Planning Comparative Study**

PROJECT DESCRIPTION: In March 2009, KFSH&RC acquired the three new innovative radiotherapy modalities: RapidArc, TomoTherapy, and CyberKnife. With these acquisitions, KFSH&RC was the first site in the world to offer state-of-the-art radiotherapy techniques combining all of these cutting-edge techniques in one single institution.

The project's aim is to perform a comprehensive treatment planning comparisons among the various radiotherapy techniques: 3D, IMRT, TomoTherapy, RapidArc and CyberKnife. This comparative study will help us recommend the right treatment planning technique and hence treatment machine for each patient undergoing radiotherapy treatment.

PROGRESS: Research in preparation. The new innovative radiotherapy systems have been commissioned and are used on a daily basis for treatment planning of patients. A number of patients have been planned

on several different treatment planning systems. A research proposal will be drafted and submitted.

PROJECT TITLE: **Incorporation of new imaging modalities (PET/CT and MRI Sim) into Radiation Treatment Planning**

PROJECT DESCRIPTION: PET/CT is a new hybrid imaging modality combining the advantages of both PET (metabolic imaging) and CT (anatomic imaging) to better localize the metabolically active cancerous tissue. Radiotherapy MRI Simulator is a new modality utilizing and adapting MRI for radiotherapy services. This project is to investigate the usefulness of these two modalities in radiation therapy simulation, treatment planning and treatment.

PROGRESS: Research in preparation. Multidisciplinary research group from different KFSH&RC departments will be formed. PET/CT software was acquired while an open MRI Simulator is being ordered. A research project will be submitted.

PUBLICATIONS

Publications in Refereed Journals

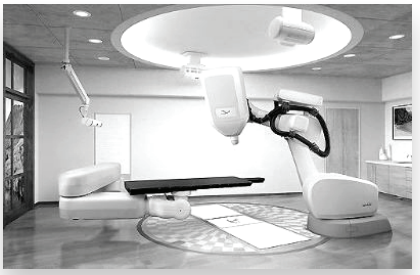
- Ahmad Nobah; Belal Moftah; Nada Tomic; Slobodan Devic, Influence of electron density spatial distribution and X-ray beam quality during CT simulation on dose calculation accuracy. *Journal of applied clinical medical physics / American College of Medical Physics* 2011;12(3):3432.
- Omar Chibani and Charlie C.M. Ma., "Photonuclear Dose From High Energy Medical Linear Accelerators", Presented at American Nuclear Society Winter Meeting, November 2011 and Published in *Transactions of the American Nuclear Society* (2011).
- Omar Chibani, Belal Moftah and Charlie Ma, "On Monte Carlo modeling of megavoltage photon beams: A revisited study on the sensitivity of beam parameters", *Medical Physics* 38, 188 (2011).
- H. I. Al-Mohammed. Measuring patient's skin dose during total skin electron therapy using MOSFET. *Biomedi Rese* 2011; 22 (1): 9–14.
- H. I. Al-Mohammed. The efficiency of using audio prompting method to regulate the patient's breathing during radiation therapy treatment of NSCLC. *IJMS*, 2011; 3(1): 1 – 6.
- Huda Ibrahim Al-Mohammed. Evaluation of clinical use of OneDose™ metal oxidesemiconductor field-effect transistor detectors compared to thermoluminescent dosimeters to measure skin dose for adult patients with acute lymphoblastic leukemia. *N A J Med Sci*. 2011, 3(8).11–17.
- H. I. Al-Mohammed. Patient Specification Quality Assurance for Glioblastoma Multiforme Brain Tumors Treated with Intensity Modulated Radiation Therapy. *I J Medi Sci*; 2011; 8(6):461–466.
- H.I. Al-Mohammed and F. H. Mayhoub Patient-specific quality assurance for the treatment of intensity modality radiation therapy of nasopharyngeal carcinoma. *JCREO*, 2011; 3(2)6–17.

Presentations at conferences and meetings

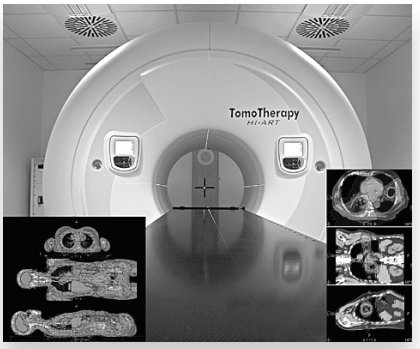
*(Presenting author *)*

- Patient specific QA. Assessment of plan Acceptability, Transfer of plan to Linac, R & V system Belal Moftah*. PhD, FCCPM during IAEA Regional Training course on Radiotherapy techniques with emphasis on imaging and Treatment planning, 9–13 October, 2011.
- Future Saudi Carbon Ion transitional Facility, Belal Moftah* PhD, FCCPM during Japanese—KFSH&RC Oncology Seminar, 2nd March 2011.

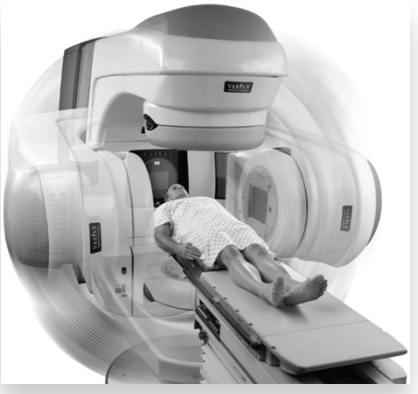
Three major radiotherapy treatment modalities at KFSH&RC.



CYBERKNIFE



TOMOTHERAPY



RAPID ARC

Radiation Safety Office

HEAD
Fareed H. Mahyoub, MSc, MIPEM

MEMBERS
Celestino Lagarde, BSc
Ibrahim Al-Gain, BSc

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-sight 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.

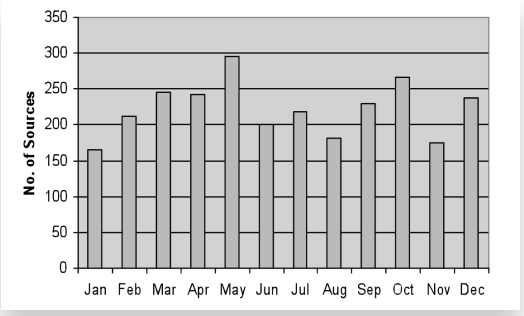


Fig. 1. Graph showing the monthly out-going packages for year 2011.

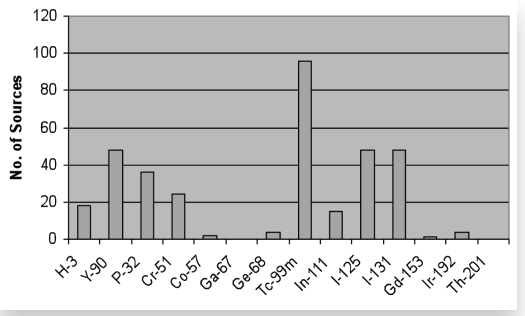


Fig. 2. Graph showing the number of imported sources of radioactive isotopes in year 2011.

RSO ACTIVITIES

For the year 2010, the RSO applied for renewal of the KFSH&RC license from KACST for the radiation practices of Nuclear Medicine, Gamma Irradiation Facility, Leak Testing, Radiation Therapy, and Scientific Research and the applications have been successfully approved. It has renewed the KACST license to import radioactive materials. Two applications for authorization to use radioactive materials were evaluated by the RSC. In radiation measurements, there were 286 incoming sources and 2672 out-going packages of radioactive materials surveyed. In the principle of "As Low as Reasonably Achievable" (ALARA), 100 investigations were carried out on staff whose occupational doses exceeded the ALARA levels; 55 thyroid bioassays were performed. Eighteen work areas and 10 equipment were surveyed for radiation and contamination levels. Five work areas were surveyed for shielding consultation and verification and 10 work areas were inspected for safety auditing. A total of 10 radioactive sealed sources were checked for inventory and 171 leak tests were undertaken. The RSO responded to 6 radiation incidents and provided 3 technical consultations. In the area of radioactive waste management, the generated radioactive wastes were managed by the decay-in storage method where 102 drums were surveyed and stored in Radioactive Waste Storage. Three practical licenses were issued/renewed by KACST. In education and training the RSO has trained 12 master students and 6 new radiation workers. The RSO has maintained its linkage within the Hospital and with national and international bodies. Three RSC meetings were coordinated and the Office continued to have linkages and collaboration with other Hospital committees.

SPECIAL PROJECT: **Issuance of Mo-99/Tc-99m Production License**

The practice license of Radio-Isotopes Production was issued by KACST in favor of the new Mo-99/Tc^{99m} project of Cyclotron & Radiopharmaceuticals Department. This is the first national facility license of its kind. The RSO was given the lead role in preparation for its licensing. The RSO has supervised the final phase before operation and assured that the facility has met the national requirements and standards by communicating with KACST. The safety measures were all evaluated to ensure compliance with national regulatory requirements for radiation safety during emergencies.

Secondary Standard Dosimetry Laboratory

HEAD
M. Gary Sayed, PhD, FACNM

MEMBERS
Nabil Iqeilan, MSc
Heba Al-Humaidan, BSc

The secondary standard dosimetry laboratory (SSDL) of the Biomedical Physics Department ensures high accuracy in radiation measurements and dosimetry for all applications of ionizing radiation. The high accuracy in measurement is maintained by successfully meeting the high standards set by the International Atomic Energy Agency (IAEA) and the World Health Organization (WHO) for radiation protection and radiotherapy levels of calibration. It gained the IAEA recognition as the first SSDL in the Kingdom to obtain the IAEA and WHO accreditation thus making it a recognized calibration laboratory in the whole world. It is also recognized by 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.

ACTIVITIES

For the year 2011, the SSDL provided calibration services to 49 instruments for KFSH&RC, 92 instruments for government agencies and hospitals, 45 instruments for private hospitals, and 855 instruments for private companies [Fig 1]. A total of 1041 radiation-measuring instruments were calibrated, inter-compared and acceptance tested. These instruments include 790 survey meters, 251 pocket dosimeters [Fig. 2]. To ensure accuracy in its calibration, the SSDL participated in the IAEA and WHO annual postal dose audit for radiotherapy energy level of calibration where it obtained a very satisfactory result.

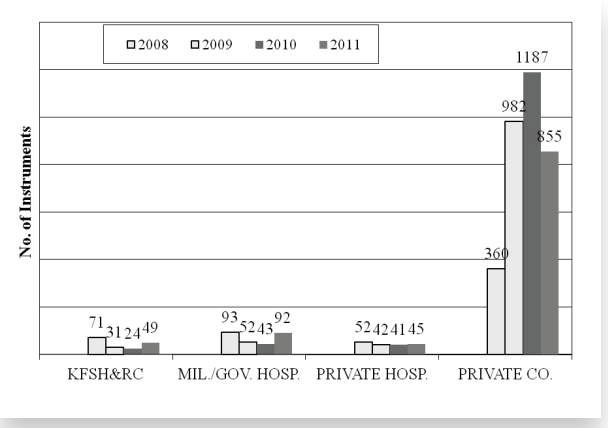


Fig. 1: Graph showing number of instruments calibrated for external facilities by the SSDL.

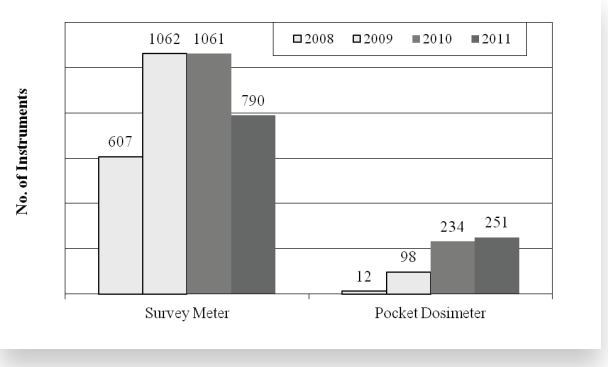


Fig. 2: Graph showing the type and number of instruments calibrated.

CARDIOVASCULAR RESEARCH PROGRAM

CARDIOVASCULAR RESEARCH PROGRAM

DIRECTOR
Coralie I. Poizat, PhD

ADMIN SUPPORT
Rita Sison

MEMBERS
Salma Mahmoud, PhD
Post Doctoral Fellow
Nadya Al-Yacoub, PhD
Post Doctoral Fellow (Grant)
Fallou Serigne Wade, PhD
Post Doctoral Fellow
Muhammad Kunhi, MSc
Research Associate
Qamar Al-Haffar, BSc
Research Assistant (Grant)
Lama Pharaon, BSc
Masters Student (Grant)
Qussay T. Marashli
Medical Student

RESEARCH SECTIONS
- Epigenetic Regulation by Nuclear CaMKII
- Genetics of Familial Dilated Cardiomyopathy
- Role of a Protein Phosphatase in Cardiovascular Diseases

THE CARDIOVASCULAR RESEARCH PROGRAM IS A NEW PROGRAM focusing on understanding molecular genetic mechanisms regulating cardiovascular disorders, more specifically cardiac hypertrophy and several forms of cardiomyopathies. The goal is to identify new pathways regulating these cardiac abnormalities. We focus on intracellular signaling pathways, transcriptional regulatory networks and epigenetic events in the normal and diseased heart. The long-term objective is to use this information for the development of therapies to improve patients' health and benefit society in general.

MAJOR ACHIEVEMENTS IN 2011

- Established an interdisciplinary Cardiovascular Research Program with bridges between basic and clinical departments, using comprehensive methodologies in cellular systems, animal models and human samples.
- Awarding of two grants from King Abdulaziz City for Science and Technology (KACST) for a two-year period.
- Developed local collaborations with the Heart Centre, the Cardiovascular & Pharmacogenomics Unit, the Developmental Genetics Unit, the Pathology Department and the Comparative Medicine Department.
- Maintained international collaborations with the Heart Institute at San Diego State University, San Diego, USA and with the La Jolla Institute for Allergy & Immunology, San Diego, USA.
- Reviewer of the Final Performance of Research Project Grant, Health Research Formula Grant Award, Pennsylvania Department of Health, USA.

RESEARCH AREAS

EPIGENETICS OF CARDIAC HYPERTROPHY

Cardiac hypertrophy is an adaptive response of the heart to a variety of cardiovascular disorders (i.e. hypertension, atherosclerosis, myocardial infarction and cardiomyopathies) characterized by an activation of a "fetal cardiac gene program" resulting in ventricular remodeling and growth of the heart. Following an initial beneficial response is a phase of abnormal growth during which the heart muscle thickens, resulting in cardiac dysfunction and increased risk to heart failure. Calcium/calmodulin-dependent protein kinases (CaMKs) are enzymes that play a role in pathological hypertrophy. We are especially interested in a nuclear isoform of CaMK, which appears to couple calcium signals to the genome in cardiac muscle. Our recent findings suggest a new mechanism regulating cardiac growth through epigenetic modifications of histone proteins. Our goal is to establish this new paradigm of transcriptional control in isolated cells, *in vivo* and to extend our observations in human failing hearts. A manuscript is currently under evaluation.

GENETICS OF FAMILIAL DILATED CARDIOMYOPATHY

Dilated cardiomyopathy (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 cardiac function. In Saudi Arabia ~70% of cases of DCM are idiopathic and a significant number are inherited and referred to as familial DCM (FDCM). In collaboration with the Heart Centre at KFSH&RC, we are enrolling families with FDCM in our study and are actively working at identifying genes responsible for the disease. For this, we are identifying the genetic risk profile of affected members of the families.

MOLECULAR GENETICS OF CARDIOVASCULAR DISEASES

Cardiovascular diseases are the major cause of death in the East and Western world. Among them, heart failure results from various conditions (i.e. long-standing hypertension, myocardial infarction and cardiomyopathies) and is associated with compromised function. There is a strong need for therapies that can alleviate or reverse the loss of contractile function that characterize a failing heart. We are addressing the role of a novel protein phosphatase (PP) in the heart. Preliminary data suggest that this protein maybe a critical novel regulator of cardiac contractility *in vivo* and in patients with coronary artery diseases (CAD). This conclusion is based from small-scale genetic association studies performed in patients with CAD, from phenotypic changes in mice deficient for the protein and from abnormal intracellular calcium transients in isolated ventricular myocytes from the heart of PP deficient mice. Future studies are designed to establish the role of PP *in vivo* and in patients with CAD from the Saudi population.

ROLE OF PHC1 IN PRIMARY MICROCEPHALY

We are working intensively on a collaborative study with Dr Fowzan Al-Kuraya (Developmental Genetics) on genetic causes of primary microcephaly (PM). Dr Al-Kuraya's group identified a novel mutation in PHC1, a member of the Polycomb repressor protein that causes PM. While Dr Fowzan's laboratory worked on the genetic aspect of the project, our group has investigated the underlying mechanism involved. Our teamwork led to a new discovery showing that the PHC1 mutation causes PM by a

new mechanism, involving defect in DNA repair pathways.

A manuscript is currently under review.

COLLABORATIONS

LOCAL

- Heart Centre, KFSH&RC (Dr Waleed Al-Habeeb)
- Cardiovascular & Pharmacogenomics Unit Genetics Department, KFSH&RC (Dr Nduna Dzimiri)
- Developmental Genetics, Genetics Department, KFSH&RC (Dr Fowzan Al-Kuraya)
- Pathology & Laboratory Medicine Department, KFSH&RC (Dr Fouad Al-Dayel)
- Comparative Medicine Department, KFSH&RC (Dr Abdullah Assiri)

INTERNATIONAL

- Heart Institute, San Diego State University, California, USA (Dr Mark Sussman)
- La Jolla Institute for Allergy & Immunology, San Diego, California, USA (Dr Nunzio Bottini)
- Biochemistry & Molecular Biology Department, University of Southern California, Los Angeles, USA (Dr Woojin An)

INVITED TALKS AND PRESENTATIONS

- Invited Speaker at the 22nd Saudi Heart Association meeting in Riyadh, Saudi Arabia, February 22, 2011, "Epigenetic Changes by Nuclear Calcium in Cardiac Diseases".
- Presenter at the Council on Basic Cardiovascular Sciences, New Orleans, July 18–21, 2011. "Epigenetic Changes by Nuclear CaMKII in the Heart".

PUBLICATION

- Cossu G, Innocenzi A, Latella L, Messina G, Simonatto M, Marullo F, Berghella L, Poizat C, Shu C-W, Wang JYJ, Puri PL. An Evolutionarily-acquired Genotoxic Response Discriminates MyoD from Myf5 and Differentially Regulates Hypaxial Versus Epaxial Myogenesis. *EMBO Reports* 2011, 12(2):164–71.

CENTRE FOR CLINICAL STUDIES &
EMPIRICAL ETHICS

CENTRE FOR CLINICAL STUDIES & EMPIRICAL ETHICS

DIRECTOR

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

MEMBERS

Abdelraheem Ahmed
Ahmed Yusuf, BSc
Basma Fayad
(Trainee, joined 23 Sept. 2011)
Eman Al-Gaai, RPh, CCRP, MHHA
(75% Flexible Employee Program)
Fadomo A. Farah
(Grant, joined 5 Nov. 2011)
Hala Amer, MD *(Grant)*
Ma. Victoria G. Ventura
(resigned June 2011)
Nada Bin Hashim, RN *(unpaid leave)*
Nessrin A. Khodr
(Grant, joined 5 June 2011)
Rajaa Hussein, RPh
Reem Al-Swayeh, RPh
Rozeena Huma, MD
(Grant, joined 4 June 2011)
Sagal Fadomo Shire, RN
(joined 29 Oct. 2011)
Saleh Al-Dgither
Sophia Sahabbil
(joined 02 Apr. 2011)
Syed N. Alvi, PhD

THE CENTRE FOR CLINICAL STUDIES AND EMPIRICAL ETHICS (CCSEE) has established itself as a national/regional centre for conducting bioequivalence, clinical, and empirical ethics studies; and for training clinical/laboratory research professionals. The activities of the CCSEE are strategically chosen to: 1) build an appropriate, self-sustaining infrastructure, and 2) concentrate on projects of direct translational values. The Bioanalytical Laboratory of the CCSEE has been accredited by the College of American Pathologists (CAP) since May 2007.

DRUG ASSAY DEVELOPMENT AND VALIDATION

No.	Drug/Chemical Entity	Analysis Method	Volume (ml)	Matrix	Range (µg/ml)
1.	Bisphenol-A diglycidyl ether	HPLC-FL	1.0	Water	0.03 - 30*
2.	Cephalexin	HPLC-UV	0.25	Human plasma	0.5–120
3.	Diclofenac	HPLC-UV	1.0	Human plasma	0.2 – 1.92
4.	Ranitidine	HPLC-UV	0.25	Human plasma	0.015 – 2.0

*nanogram/ml

CLINICAL

PROJECT TITLE: **Does Vitamin D improve Glycemic Control in Type II DM? A Double Blind Randomized Controlled Trial**

RAC # 2101 039

PROJECT DESCRIPTION: 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. 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: funded by the National Plan for Science, Technology, and Innovation (NPSTI), recruiting.

PROJECT TITLE: **Effect of Vitamin D oral supplements on OH Vitamin D Levels: A Randomized Controlled Trial**

RAC # 2101 041

PROJECT DESCRIPTION: 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 blind, 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. The information obtained will be important for scientists in the field, managing physicians, and policy makers.

STATUS/PROGRESS: funded by the National Plan for Science, Technology, and Innovation (NPSTI), ongoing.

PROJECT TITLE: **The Placebo Effect may Involve Modulating Drug Bioavailability**

RAC # 2101 105

PROJECT DESCRIPTION: The total effect of a medication is the sum of its drug effect, placebo effect (meaning response of placebo), and their interaction. Current interpretation of clinical trials (the gold standard of evidence-based-medicine) assumes no interaction, and the mechanism(s) underlying such interaction have not been fully explored. One possibility is that the placebo effect may modulate drug bioavailability. Using caffeine as a model drug (KACST ARP-26–45), we have recently shown that the placebo effect of caffeine ingestion prolongs caffeine half life. Due to the novelty of this finding and its important

clinical practice and clinical research implications, it needs to be confirmed in another set of subjects and extended to additional drugs. The results of the study are expected to further our understanding of the mechanism of action of a widely used medical intervention, i.e., placebo. The results will be important for both clinical practice and clinical research.

STATUS/PROGRESS: submitted for external funding, ongoing.

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

RAC # 2101 100

PROJECT DESCRIPTION: 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 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: Funded by the Long-Term Comprehensive National Plan for Science, Technology and Innovation (NPSTI), ongoing.

PROJECT TITLE: **Salivary testosterone level in healthy male Arabs**

RAC # 2071 081

PROJECT DESCRIPTION: Accurate determination of biologically-available testosterone levels is fundamental to studying physiological and pathophysiological androgenic status. Measuring salivary testosterone level is convenient, non-invasive, and accurate. We have developed and validated a liquid chromatography mass spectrometery assay for salivary testosterone. We are using it to determine normal testosterone levels in adult Arab males of different age groups.

STATUS/PROGRESS: recruiting.

PROJECT TITLE: **Vitamin D Content in Fortified Liquid Milk in Saudi Arabia: A Cross Sectional Study**

RAC # 2100 014

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

STATUS/PROGRESS: ongoing.

PROJECT TITLE: **Does Vitamin D reduce Risk of Developing Type II DM in Pre-diabetes? A Double Blind Randomized Controlled Trial**

RAC # 2101 040

PROJECT DESCRIPTION: 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 the development of type II DM has not been established. We plan to conduct a 2 year, double blind, randomized,

placebo controlled trial on the effect of vitamin D3 supplement on the incidence of type II DM in high risk individuals. The study will test the hypothesis that vitamin D deficiency and the development of type II DM are causally related and that vitamin D repletion can prevent type II DM. The contribution of improved insulin secretion vs action will be explored. The information obtained will be important for scientists in the field, managing physicians, and policy makers.

STATUS/PROGRESS: submitted for external funding.

PROJECT TITLE: **Magnitude of Change in 25 OH Vitamin D3 Levels After Vitamin D3 Supplementation: A Prospective Study**

RAC # 2101 042

PROJECT DESCRIPTION: Vitamin D deficiency is common in Saudi Arabia and world wide. 25 OH vitamin D level is the best indicator of vitamin D status. The determination of the appropriate dose of vitamin D supplement is essential for management of vitamin D deficiency as well as for designing vitamin D fortification programs. The increments in 25 OH vitamin D levels following various doses of vitamin D supplement for different genders, body weights, and starting 25 OH vitamin D level have not been well defined. The time course of depletion of repleted vitamin D stores is also not known. We plan to conduct a double blind randomized study on 32 cohorts to determine levels of 25 OH vitamin D following supplementation with different doses of vitamin D3 for 5 months and their withdrawal for 3 months. The study will establish the optimal supplement dose for various demographic groups and the time course of depletion of vitamin D stores. The information obtained will be important for scientists in the field, managing physicians, and policy makers.

STATUS/PROGRESS: submitted for external funding.

PROJECT TITLE: **Hyponatremia in Thyroid Cancer Patients Undergoing RAI Therapy: A Prospective Study**

RAC # 2101 050

PROJECT DESCRIPTION: Patients with differentiated thyroid cancer are instructed to withhold thyroid hormone treatment, follow a low salt (iodine) diet, and increase fluid intake, in preparation for/shortly after radioactive iodine (RAI) therapy. Such instructions in combination with potential nausea caused by RAI, and anxiety may result in serious iatrogenic hyponatremia in patients who are in isolation. We plan to study the incidence and severity of hyponatremia in a cohort of 220 thyroid cancer patients around the time they are cleared for discharge after RAI therapy. Discharge sodium level will also be correlated with pre RAI dosing sodium level, TSH level, age, and estimated fluid intake; and compared between males and females and among patients with relevant co-morbidities (such as DM). The study is expected to provide important information relevant to the management of thyroid cancer patients undergoing RAI therapy.

STATUS/PROGRESS: recruiting.

PROJECT TITLE: **Molecular Characterization of Generic Defect in Family With Johnson McMillin Syndrome**

RAC # 2110 036

PROJECT DESCRIPTION: Johnson-McMillin syndrome has autosomal dominant inheritance pattern but so far unidentified gene/locus. Identification of novel causative genes involved in Mendelian disorders is usually performed by linkage or genome-wide association studies, which require recruitment of large families. A trio-based exome sequencing is a powerful alternative approach to identify new candidate genes in genetic diseases. It involves sequencing of the subset of the human genome that is protein coding in parent-offspring trios in which only the offspring is affected. We plan to study the exons of a patient with Johnson-McMillin syndrome and his parents using trio-based genome sequencing in order to identify the causative mutation in this syndrome. The study is expected to advance scientific knowledge and may help in genetic counseling and medical management of the family.

STATUS/PROGRESS: ongoing.

PROJECT TITLE: **Clinical & Molecular Characterization of Family with Steroid Hormones Synthesis Defect**

RAC # 2110 036

PROJECT DESCRIPTION: We plan to study a family with adrenal and gonadal hormone deficiency and peculiar clinical presentation by direct sequencing of genes coding for steroid genesis. We expect the defect to be in the gene coding for 17 hydroxylase/17–20 lyase activities. Other potential candidates include cholesterol side cleavage enzyme, StAR, P450 oxidoreductase, SF-1, and DAX-1. We will also determine whether there is genotype-phenotype correlation. If a novel mutation is found, it will be further characterized by *in vitro* functional studies.

STATUS/PROGRESS: ongoing.

PROJECT TITLE: **Interaction between drug and placebo effects: randomized placebo-controlled trials may not be accurate in determining drug effect size**

RAC # 2111 001

PROJECT DESCRIPTION: 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 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 clinical 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. The results of the study are expected to further our understanding of a widely used medical intervention, i.e., placebo, and help assess the appropriateness of randomized clinical trials in determining the size of drug effect.

STATUS/PROGRESS: submitted for external funding, ongoing.

EMPIRICAL ETHICS

PROJECT TITLE: **Ethical Approval of Human Subjects Research Published in Saudi medical Journals**

RAC # 2051 030

ABSTRACT: We evaluated documentation of ethical conduct (obtaining IRB approval and consent and following ethical guidelines) of human subject research studies (HSRS) published in Saudi medical journals. HSRS were classified as retrospective, prospective non-interventional, interventional, or survey/interview. 1838 HSRS were identified (36.6% retrospective, 26.2% prospective non-interventional, 18.6% interventional); 0.9% documented following ethical guidelines, with a higher rate (P=0.003) for post year-2000 studies (1.7%). 8.6% of 821 studies requiring IRB approval and informed consent, documented fulfilling both requirements, with a higher rate (P<0.0001) for interventional studies (19.4%), post-year 2000 studies (19.7%), and studies performed outside Saudi Arabia (15.9%). The low documentation rate suggests editor's lack of rigor and/or investigators' ignorance of guidelines. The lower documentation rate for non-interventional studies and for studies conducted in Saudi Arabia suggests unawareness of the scope of human subject research, whereas the higher documentation rate after year 2000 suggests an on-going improvement.

STATUS/PROGRESS: completed.

PROJECT TITLE: **Patients' perception of informed consent: function and required information**

RAC # 2081 002

ABSTRACT: The informed consent (IC) is an established ethical and legal requirement for providing medical care. The "function" of IC and the type and extent of information to be provided continue to be controversial. We explored perception of KFSH&RC adult patients of current and should-be, function and

type and extent of information of procedure-specific, explicit, written informed consent. 650 patients who had undergone a consent-requiring procedure in the previous 6 months or were planning to have one in the following 3 months were invited to participate in the study in clinics waiting area. 496 (76.3%) patients provided evaluable information (29 did not understand the study and 125 did not consent/have time). Mean (SD) age was 38.4 (12.6), 50% were females, 97% Saudis, 34% held professional, technical, or managerial occupation and 29% were housewives, 45% had a Bachelor or higher education, 38% already had the procedure, and 76% had self-declared chronic disease. Respondents ranked 10 statements related to perceived current and should-be function of IC from 1 (most reflective) to 10. Mean (SD) scores ranged from 3.9(2.2) for "to inform patient of what will or might happen" to 8.5(2.2) for "a meaningless routine paperwork" for perceived current function (n=474) and from 3.0(2.2) for "to help patients make their own rational medical decision" to 8.9(1.6) for "a meaningless routine paper work" for should-be function (n=461). Respondents also completed a 5 point Lickert scale on their perception of whether the following information are currently provided and should-be provided in IC: responsible practioner (name and title, place of training, years of experience, number of procedures performed, success rate, name and title of anesthesiologist, name of assistants/trainees), benefits/advantages (minor, moderate, major), risks (minor, moderate, major with and without frequency), management of complications (provided or not, where, cost), available alternatives (city, country, worldwide), description of procedure (name, simple, detailed), and post-procedure issues (recovery time, feeding, urine and bowel care, pain/discomfort, special requirements, return to work). In all instances, it was perceived that more information should be provided than as currently provided.

STATUS/PROGRESS: completed.

PROJECT TITLE: **Written Versus Verbal Information in Consenting for Consenting for Thyroidectomy: Patient Satisfaction & Information Retention**

RAC # 2081 047

ABSTRACT: A written informed consent is an ethical and legal requirement for surgical procedures. The information required for consenting can be provided either in a verbal format (VF) or in a written format (WF). Our aim was to compare the two formats in relation to satisfaction, information retention, and perception of the role consenting in patients undergoing thyroidectomy. 100 adult medically stable patients scheduled for thyroidectomy were enrolled in a block-randomized trial to receive either VF or WF consenting. Post-operatively, patients completed a questionnaire of three parts: evaluating 12 statements on patient satisfaction using a 5-point Likert scale (1 strongly disagree, 5 strongly agree), answering 17 questions on indication, procedures, and risks of thyroidectomy (score 0–17), and ranking 10 statements (1 most agreeable, 10 least agreeable) on the role of informed consent. The time spent on the two formats was also compared. Data were reported as mean (SD) and were evaluated by unpaired two-tailed t-test unless indicated otherwise. 85 respondents (43 VF and 42 WF) completed the post-operative questionnaire after a mean (SD) 59.3 (47.4) days from consenting. Their age was 37.6 (11.8) years, 75.3% were females, 95.2% were Saudis, 56.6% had ≤ secondary school education, and 41.5% were house wives. There were no significant differences between VF and WF groups regarding patient satisfaction [4.66 (0.49) versus 4.61 (0.37), P = 0.58], retention of information scores [8.95 (2.6) versus 9.41 (3.3), P = 0.50], time spent in obtaining consent [10.8 (9.2) versus 11.6 (7.1) minutes, P = 0.66], time between consenting and completing the questionnaire [60.1 (46.5) versus 58.5 (48.9) days, P = 0.88], or ranking of individual statements regarding informed consent role (P = 0.1–0.99), except for the statement "The consent process scared me unduly" [4.37 (1.24) with VF versus 3.76 (1.38) with WF, P = 0.03]. However, satisfaction level was higher in females [4.69 (0.36) versus 4.47 (0.57) in males, P = 0.04], illiterates [4.89 (0.13) versus 4.73 (0.27) with ≥ college education and 4.53 (0.51) with ≤ secondary school education, P = 0.02 (Kruskal-Wallis test)] and in patients with < 30 days between consenting and completing the questionnaire [4.79 (0.26) versus 4.56 (0.48) in ≥ 30 days, P = 0.02]. Further, retention of information scores was significantly higher in patients with ≥ college

education [10.5 (2.91) versus 9 (1.5) in illiterates, and 8.26 (2.83) ≤ secondary school education, P = 0.005 (Kruskal-Wallis test)] and in employed participants [10.1 (3.06) versus 9.8 (3.19) students, 8.5 (2.68) in housewives, and 7.44 (2.13) in unemployed, P = 0.03 (Kruskal-Wallis test)]. We conclude that: 1) patient satisfaction, retention of information, and perception of role of consenting were not influenced by the way the consenting information was presented to patients, 2) female gender, illiterates along with high level of education, and shorter time intervals between consenting and completing the questionnaire, are associated with higher satisfaction, 3) level of education and occupation status were associated with higher degree of information retention.

STATUS/PROGRESS: completed.

PROJECT TITLE: **Consenting options for organ donation: A survey of the opinion and references of Saudis**

RAC # 2071 068

ABSTRACT: Posthumous organ procurement is hindered by the consenting process. Several consenting systems have been proposed. There is limited information on public relative attitudes towards various consenting systems, especially in Middle Eastern/Islamic countries. We surveyed 698 adult Saudis attending the outpatient's clinics of a tertiary care hospital in Saudi Arabia. Personal preference and perception of norm regarding consenting options for posthumous organ donation were explored. Participants were asked to rank the following options from 1 (most agreeable) to 11: no-organ-donation, presumed consent, informed consent by donor-only, informed consent by donor or surrogate, and mandatory choice; the last three without or with medical or financial incentive. The 11 options were presented to participants in randomly. Mean (SD) age of respondents was 32 (9) year, 27% were males, 78% were self-perceived as healthy, 50% were patients' companions, 60% had college or higher education, and 20% and 32%, respectively, knew an organ donor or recipient. No-organ-donation option was among the top three choices for preference of only 17% of respondents, with an overall median [25%, 75% quartile] score of 11 [6,11]. Mandated choice option was among the top three choices of 54% of respondents, with an overall median score of (3 [2,6]), and was preferred over the options of donor or surrogate informed consent (4 [2,7], p<0.001), donor –only informed consent (5 [3,7], p<0.001), and presumed consent (7 [3,10], p<0.001). The addition of a financial or medical incentive reduced the preference for mandated choice option to 7 [4, 9], p<0.001 and 5 [3,8], p<0.001, respectively; for donor-only informed consent option to 8 [6,10], p<0.001 and 5 [3,7], p=0.56, respectively; and for donor or surrogate informed consent option to 7 [5,9], p<0.001 and 5 [3,7], p=0.004, respectively. Distributions of preference and perception of norm among the 11 options were not statistically different. Compared to males, females more dis-preferred mandated choice with financial incentive option (6 [3,8] vs. 8 [4,9], p<0.001), and less dis-preferred mandated choice with medical incentive option (7 [4,9] vs. 5 [2,7], p<0.001), and were less likely to perceive donor or surrogate informed consent as the norm (3 [1,6] vs. 5 [3,7], p<0.001). There was no association between consenting options score and age, health status, education level, or knowing an organ donor or recipient. We conclude that: 1) Most respondents were in favor of posthumous organ donation, 2) mandated choice system was the most preferred and presumed consent system was the least preferred, 3) financial (especially in females) and medical (especially in males) incentives reduced preference, and 4) distributions of preference and perception of norm were not different.

STATUS/PROGRESS: completed.

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 (the acceptance of placebo use in medicine abortion, and organ donation). Q-sets have been constructed and examined for reliability and validity. The extent people use ethical principles other than those described in the four-principles-plus-scope approach (i.e., respect for autonomy, beneficence, non-malificence, and justice) will be examined. The association of various demographic factors with the identified models and the effect of formal ethical education will be studies. We will also explore the stability of the identified models/points of equilibrium over time, within demographic groups, and across topics. The results are expected to have important contributions to empirical 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 or 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.

PROJECT TITLE: **Saudi End of Life Priorities 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. 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.

PUBLICATIONS

- Hunida E Abdulhameed. Muhammad M. Hammami & Elbushra A. Hameed Mohamed. Disclosure of Terminal Illness to Patients and Families: Governing Code in Islamic & Arabic Countries. *J MED* Ethics. 2011;37:472–475.
- Eman A Al-Gaai, Muhammad M. Hammami, and Manal A Eleidan. Documentation of Ethical Conduct of Humak Subject Resaerch Published in Saudi Journals. *EMHJ*. In press.
- Syed N. Alvi and Muhammad M. Hammami. Validated HPLC method for Determination of Caffeine Level in Human Plasma Using Synthetic Plasma: Application to Bioavailability Studies. *Journal of Chromatographic Science*. 2011; 49:292–296.
- Rajaa Hussein and Muhammad M. Hammami. Determination of Ketoprofen Level in Plasma by Fully Validated HPLC Assay. *International J of Pharmacy & Technology* (*IJPT*) (eISSN:0975–766X; *CODEN:IJPTFI*) Volume-3 Jan-March 2011.
- A R Hussain, M Ahmed, S O Ahmed, P Manogran, Syed N Alvi, L C Platanias, K S Al Kuraya, Shabuddin. Thymoquinone suppresses growth and induces apoptosis via generation of reactive oxygen species in primary effusion lymphoma, *Free Radical Biology and Medicine* 50:8 (2011) 978.
- Saleh Al Dghaither, Ahmed Yusuf, Muhammad Hammami, Fluconazole: Stability and analysis in human plasma by simple high performance liquid chromatography, Saleh Al Dghaither, Ahmed Yusuf, Muhammad Hammami, FABAD: *Journal of Pharmaceutical Sciences* 2011; 34:77–81.
- Reem Saleh Al Swayeh, Syed Alvi, and Muhammad M. Hammami: Ampcillin Analysis by Fully Validated HPLC in Human Plasma, *Journal of Analytical Chemistry*. 2011;10:2.

CELL BIOLOGY

CELL BIOLOGY

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

ADMIN SUPPORT
Rita Sison
Camelia Touzinte
Cheryl Mijares *Grant*

The history of cell biology goes back to the time of the cell theory proposed by Schleiden & Schwan in 1839. Since then, numerous and still emerging concepts in cell biology has transformed the way we treat diseases. Although human and animal genome, proteome, metabolome, etc. have identified many genes and protein necessary for the continued healthy existence and survival of whole animals, knowledge about many of these whether structural, functional or temporal is still seminal. Knowledge of basic molecular mechanisms of "normal" cellular life and controlled cellular death are largely lacking and this leaves many potential targets for therapies essentially undiscovered, hence the necessity to establish the Department of Cell Biology at the Research Centre of King Faisal Specialist Hospital and Research Centre.

The Department of Cell Biology 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 diabetes retinopathies.

The research activities of the sections under of the Department of Cell Biology will be described in the subsequent sections that follow.

Cardiovascular Biology Section

Xenotransplantation Research unit

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

MEMBERS
Reem Al Hejailan
Soad Saleh
Ranjit Parhar, PhD
Razan Bakheet
Mohammed Quttainah, PhD
Xingyang Zhang, MD
Mohammed Al Halabi Grant

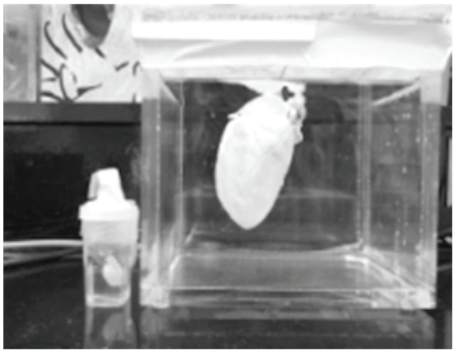
This section is devoted to finding viable solutions to the need for health interventions in Cardiovascular patients who are no longer responding to pharmaceutical and/or surgical intervention. Currently there are very limited alternatives to heart transplantation, and the number of patients with this disease is increasing annually.

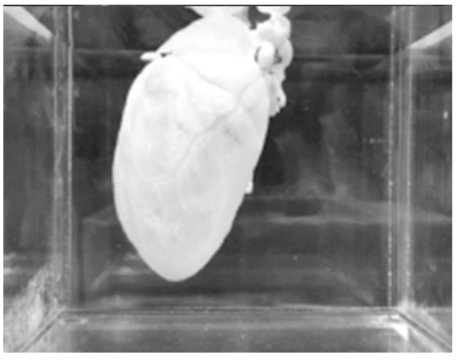
Due to the profound lack of donor organs for transplantation, many patients with end-stage heart failure succumb to fatalities during the wait for a suitable organ replacement. Xenotransplantation provides a viable alternative for such replacement. However, many immunological and physiological barriers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

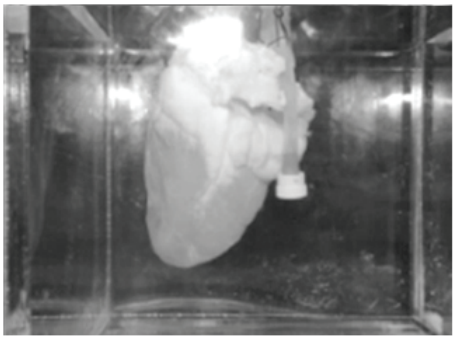
SECTION'S ACTIVITIES

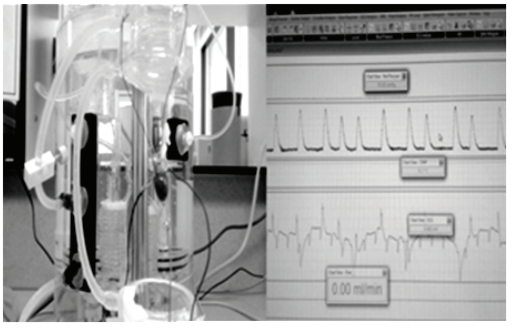
The Cardiovascular Unit has been active in researching the mechanisms which prevent successful xenotransplantation. The results of our endeavors have identified innate immune cells, namely the human naive neutrophils and NK cells, of the recipient as major players in recognizing xenoantigen independently 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 xenorecognition by innate immune cells using serial analysis of gene expression.

A second line of research is the use of vaccinia virus complement modulatory protien 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 examining the possibility of reengineer a decellularized xenogeneic whole heart with intact vasculature and three-dimensional scaffold by recellularizing with EST in animal models.





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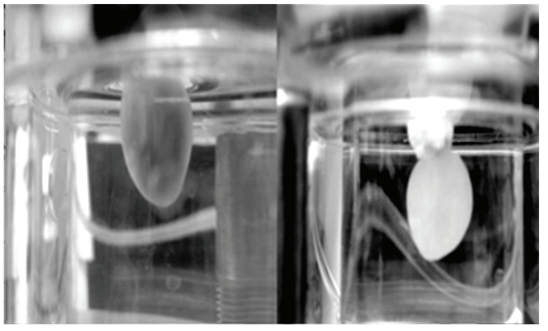
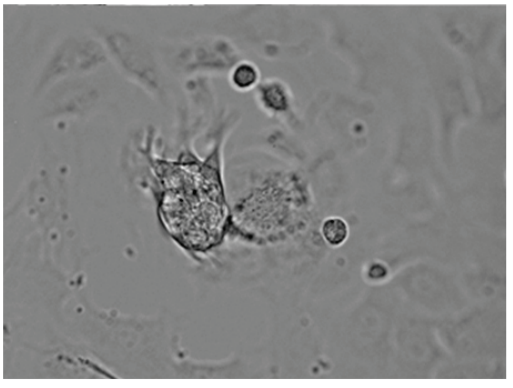
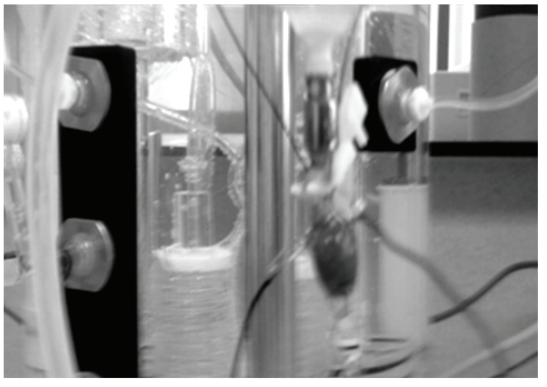




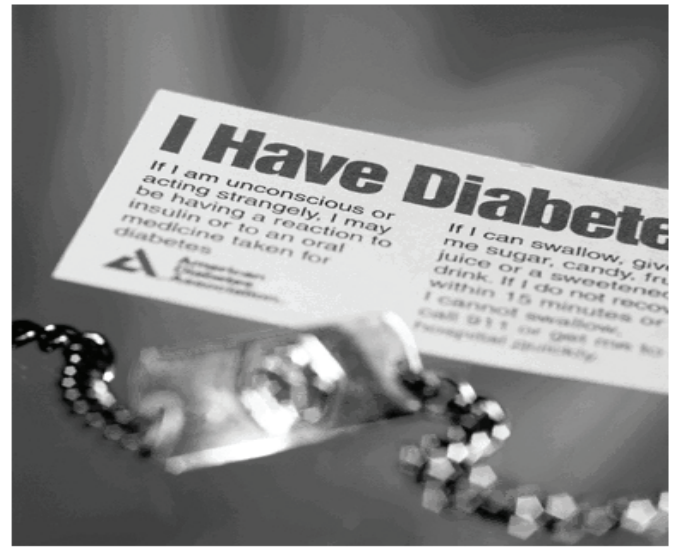


Diabetes Research Section

HEAD
Katherine S. Collison, PhD

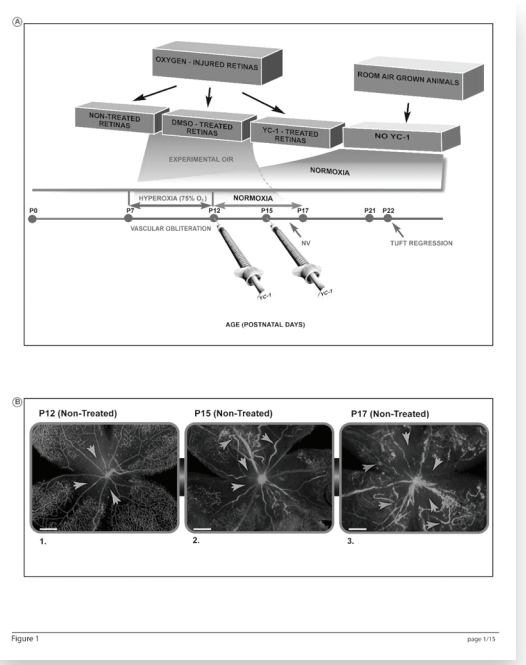
MEMBERS
Angela Inglis
Nadine Makhoul
Bernard Andres
Rana Al-Rabiah
Marya Zia Zaidi *Grant*
Rosario Ubungen *Grant*
Jennifer Thiam *Grant*

The global prevalence of type 2 diabetes (T2D) was 284 million in 2010 (6.4% of the world population), and Saudi is one of the most affected countries, spending over 20% of its total health expenditure on this disease alone. Our research program examines the contribution specific micro- and macronutrients to the development of glucose deregulation, insulin resistance and obesity. Diabetes is often a risk factor for other metabolic diseases, such as Non-Alcoholic Fatty Liver Disease (NAFLD); and patients with T2D are more likely to suffer from age-related cognitive impairment. It is generally agreed that whilst there may be a genetic component to T2D, the increasing prevalence of this disease and associated risk factors is due to increased consumption of cheap, energy-dense and nutrient-poor foods; together with a reduction in physical exertion and exercise. This may be particularly apparent in the younger generation.



SECTION ACTIVITIES

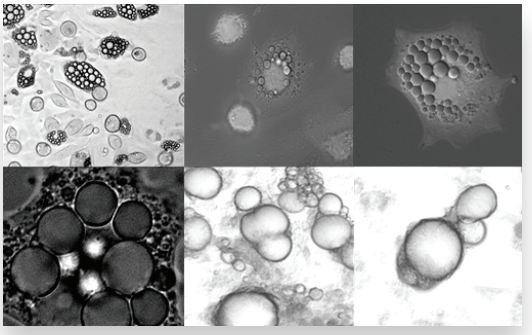
We have identified four major recent additions to the global diet which we believe have contributed enormously to the growing epidemic of Diabesity. We have shown how High Fructose Corn Syrup (HFCS) disrupts liver function, causing increased fatty deposition, the generation of reactive oxygen metabolites, mitochondrial disruption and endoplasmic reticulum stress. We have also shown how HFCS alters gene expression, which can further be modulated by the ubiquitous food additive Monosodium Glutamate (MSG). Our animal models have demonstrated how Trans Fat can disrupt liver gene expression and promote fatty liver disease, and recently we have turned our attention to the artificial sweetener Aspartame, which we show can impair glucose homeostasis, which may directly affect Diabetics and dieters who use so-called "Diet" products. Our work, though largely animal-model based, has considerable relevance to human health, and has resulted in a number of high-impact publications.



COLLABORATIVE RESEARCH

1. **Animal models for diabetes retinopathies:**
This work is in collaboration with CMD and KKISH and investigates hypoxia/hyperoxia- induced retinopathies *in vitro* and *in vivo* as a model for diabetes retinopathy. The work has lead to the discovery of a small molecule inhibitor of HIF-1 alpha that can reverse the effect of hypoxic/hyperoxic insult on the retina. Patent for the use of this small molecule is already filed. A Biotechnology grant has already been awarded for the continuation of this work.

2. **Role of KLF3 in fatty acid β-Oxidation: towards combating obesity.**
This collaborative work focuses on extending the finding that mutation in the Krüpple like transcription factor (KLF3) in C elegans which cause fat accumulation may also occur in mammals through similar mechanism(s).



Allergy And Medical Aerobiology Section

HEAD
Syed M. Hasnain, PhD, FACAAI, FAAAAI

MEMBERS
Abdulrahman Al-Suwaine, PhD
Halima Al-Sini
Abdulrahman Al-Sobhi
Alanoud Al Qassem
Mubarak Al Enazi
Salma Kabbara *Grant*

Allergy and asthma in both children and adult can be caused by many allergenic pollen grains from weeds, trees and grasses. World allergenic pollen flora varies in their nature and quantity from place to place and fluctuates with geography and climate.

Our mission is to seek, search and advance the scientific knowledge of environmentally induced respiratory allergic diseases, provide support for proper diagnosis, treatment and prevention of such diseases and to participate in graduate and post graduate training and education program.

SECTION ACTIVITIES

- Research on Indigenous causes of increasing prevalence of allergies and asthma in the country
- An Environmental, Epidemiological and Clinical Investigation of Allergy and Asthma in relation to Outdoor and Indoor Aeroallergens Saudi Arabia.
- Continuation of our endeavors for the production of allergy diagnostic kits for the Middle East Region (based on successful clinical trial conducted last year).
- The development of a community oriented services program for the people of Saudi Arabia.

RAC APPROVED PROJECTS

PROJECT TITLE: **Towards allogenizing a xenograft. "The Use of Rat Embryonic Stem Cells in Decellularized Rat Hearts"**

RAC # 2110 011

DESCRIPTION: The Cardiovascular Unit has been active in researching cellular mechanisms in xenograft rejection *in vitro*.

PROGRESS: Progress has been made in decellularizing the rodent hearts. This is an on-going project and achievements will be discussed at the end of the study.

PROJECT TITLE: **Inflammatory Modulator Protein Vaccinia Virus Complement Control Protein (VCP): Potential Therapeutic in CVD**

RAC # 2050 046

DESCRIPTION: This project aimed at up scaling the production of VCP from mammalian cells. VCP inhibits complement activation and xenograft rejection. A recent patent for the use of VCP in xenotransplantation was granted. Canadian patent number: 2374681

PROJECT TITLE: **Role of excitatory amino acids in Trans fat-induced obesity, dyslipidemia, Hepatic Steatosis and Cognitive Impairment**

RAC # 2092 028

PROGRESS: We have previously identified trans fat as a direct contributor to hepatic steatosis, and that Monosodium Glutamate (MSG) further alters hepatic gene expression and exacerbates Trans-fatty liver disease in an animal model. We next examined the interaction between two commonly consumed food additives which have previously been linked with neuroendocrine damage, and we found evidence for impairment of glucose homeostasis and spatial cognition in Aspartame-treated animals. The combination of Aspartame and Monosodium Glutamate showed more impairment in glucose homeostasis than Aspartame alone, suggesting that the effects of these excitotoxins are additive. Aspartame is rapidly metabolized into methanol, phenylalanine and aspartate. N-methyl D-aspartate (NMDA) receptors, which are concentrated in the central nervous system in areas which control energy balance (the hypothalamus) and learning (hippocampus), have binding sites for glutamate and aspartate. This may explain why the effects of Aspartame and Monosodium Glutamate appear to be additive. We have published 2 manuscripts this year and are preparing two further manuscripts for publication.

PROJECT TITLE: **Acceptability of experimental N-methyl D-aspartate (NMDA) receptor antagonist CGP39551 as an orally active competitive glutamate and aspartate receptor blocker in rodents**

RAC # 2110 010

DESCRIPTION: As a continuum of RAC 2092 028, we now examine the feasibility of using a specific NMDA receptor agonist CGP37849 to interfere with MSG and Aspartame-induced disruption of glucose homeostasis, thus proving that the effects of aspartame & MSG are mediated by NMDA receptors. This Pilot study tests the acceptability of CGP37849 within our research model.

PROGRESS: We are still testing the CGP37849 drug for possible side effects. So far it has been reasonably well tolerated and has not altered food or water intake, body weight or behavior.

MAJOR FINDINGS: Will be discussed at the end of the study, which is still on-going.

PROJECT TITLE: **Diet-Induced Metabolic Syndrome, Cardiovascular Disease & Cognitive Decline effect of Trans-hydrogenated fat intake on insulin Resistance, Hyperlipidemia, Inflammation & cognition in a Rodent Model**

RAC # 2060 077

Biotechnology Spinoffs:
The department together with others has been successful in spinning off two projects into pre commercial company establishment with the full

support of the National Biotechnology initiative from King AbdulAziz City for Science and Technology (KACST) through Bio-incubator track.

These are as follows:

- Allergotek Diagnostic and Therapeutic Program (ADTP) (Approved Budget: SAR3,348,000)
- Reagent Production Project (RPP) (Approved Budget: SAR2,966,000)

PROJECT TITLE: **Isolation, Purification and Immunochemical Characterization of Allergenic Protein(s) from Amaranthus viridis Pollen Grains**

KACST ARP 27–11, RAC Project #2050 029. In collaboration with proteomic's unit of BMR (Dr. Ayodele Alaiya) and King Khalid University Hospital (Dr. Mohammed Osman Gad-El-Rab), Riyadh.

PROGRESS: Completed in June 2011

MAJOR FINDINGS: The study confirmed that there were similarities and differences in the proteins and there were positive and negative SPTs, Two indigenous species (local weeds) showed very similar "protein patterns" compared to the other four commercial varieties. Likewise, in the clinical SPT, the two indigenous Amaranthus allergens showed similar reaction patterns different from the 4 commercial allergens. We have identified some protein spots on 2-DE gels that should be further validated in order to support their usefulness as potential Amaranthus biomarkers for the diagnosis and therapy monitoring of allergy patients.

PROJECT TITLE: **An allergological study of various indoor allergens in homes of Saudi Arabia**

RAC # 2100 031

DESCRIPTION: A project proposal to analyze various house dust mites in various cities of Saudi Arabia has been submitted and preliminary approved by KACST thru ORA. This project will be first of its type to include all major cities and Saudi homes in 6 different cities in Saudi Arabia. My role will be Principal Investigator. This is an In-House project and Ministry of Education and/or Directorate of Education will be participating.

PROGRESS: Preliminary approved by KACST

DEPARTMENTAL PUBLICATIONS

- 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*, April 3, 2012.
- DeNiro M, Falah H. Al-Mohanna and Futwan A. Al-Mohanna. Targeting Reactive Gliosis Rescue the Neurosensory Retina during Retinal Vasculopathies. *Plos One* 2012. In press.
- Collison KS, Zaidi MZ, Saleh SM, Makhoul NJ, Inglis A, Burrows J, Araujo JA, Al-Mohanna FA Nutrigenomics of hepatic steatosis in a feline model: effect of monosodium glutamate, fructose, and Trans-fat feeding. *Genes Nutr.* 2011 Dec 6. [Epub ahead of print].
- DeNiro M & and Futwan Al-Mohanna. Dual Targeting of Retinal Vasculature in the Mouse Model of Oxygen Induced Retinopathy. *The Open Diabetes Journal*, 2011, 4, 60–74. 1876–5246/11 2011.
- Collison KS, Zaidi MZ, Maqbool Z, Saleh SM, Inglis A, Makhoul NJ, Bakheet R, Shoukri M, Al-Mohanna FA. Sex-dimorphism in cardiac nutrigenomics: effect of transfat and/or monosodium glutamate consumption. *BMC Genomics*. 2011 Nov 12;12:555.
- DeNiro M & Futwan Al-Mohanna. Reversal of Retinal Vascular Changes Associated with Ocular Neovascularization by Small Molecules: Progress toward Identifying Molecular Targets for Therapeutic Intervention. *The Open Diabetes Journal*, 2011, 4, 75-95 75. 1876-5246/11 2011.
- Collison KS, Zaidi MZ, Saleh S, Inglis A, Mondreal R, Makhoul NJ, Bakheet R, Burrows J, Milgram NW, Al-Mohanna FA. Effect of transfat, fructose and monosodium glutamate feeding on feline weight gain, adiposity, insulin sensitivity, adipokine and lipid profile. *British Journal of Nutrition* 2011, Mar 24:1-10.

- Deniro M, Al-Halafi A, Al-Mohanna FH, Alsmadi O, Al-Mohanna FA. Pleiotropic Effects of YC-1 Selectively Inhibits Pathological Retinal Neovascularization and Promotes Physiological Revascularization in a Mouse Model of Oxygen-Induced Retinopathy. *Mol Pharmacol*. 2010 Mar;77(3):348–67.
- Collison KS. Response to "Effect of Dietary Monosodium Glutamate on HFCS-Induced Hepatic Steatosis- Additional Information" Letter-to-the-Editor, *Obesity* (Silver Spring), May 2011.
- Alzahrani AS, Zou M, Baitei EY, Parhar RS, Al-Kahtani N, Raef H, Almahfouz A, Amartey JK, Al-Rijjal R, Hammami R, Meyer BF, Al-Mohanna FA, Shi Y. Molecular characterization of a novel p.R118C mutation in the insulin receptor gene from patients with severe insulin resistance. *Y. Clin Endocrinol* (Oxf). 2012 Apr;76(4):540-7.
- Zhang J, Bakheet R, Parhar RS, Huang CH, Hussain MM, Pan X, Siddiqui SS, Hashmi S. Regulation of fat storage and reproduction by Krüppel-like transcription factor KLF3 and fat-associated genes in Caenorhabditis elegans. *J Mol Biol*. 2011 Aug 19;411(3):537–53.
- Zou M, Baitei EY, Alzahrani AS, Parhar RS, Al-Mohanna FA, Meyer BF, Shi Y. Mutation prediction by PolyPhen or functional assay, a detailed comparison of CYP27B1 missense mutations. *Endocrine*. 2011 Aug;40(1):14–20.
- Amartey JK, Parhar RS, Shi Y, Al-Mohanna F. Preliminary evaluation of two radioiodinated maleimide derivatives targeting peripheral and membrane sulfhydryl groups for in vitro cell labeling. *Appl Radiat Isot*. 2011 Jan;69(1):163-70.
- Raef H, Al-Rijjal R, Al-Shehri S, Zou M, Al-Mana H, Baitei EY, Parhar RS, Al-Mohanna FA, Shi Y. Biallelic p.R2223H mutation in the thyroglobulin gene causes thyroglobulin retention and severe hypothyroidism with subsequent development of thyroid carcinoma. *J Clin Endocrinol Metab*. 2010, 95(3):1000-6.

* some of the publications listed may have also been reported by other departments due to the collaborative nature of the work.

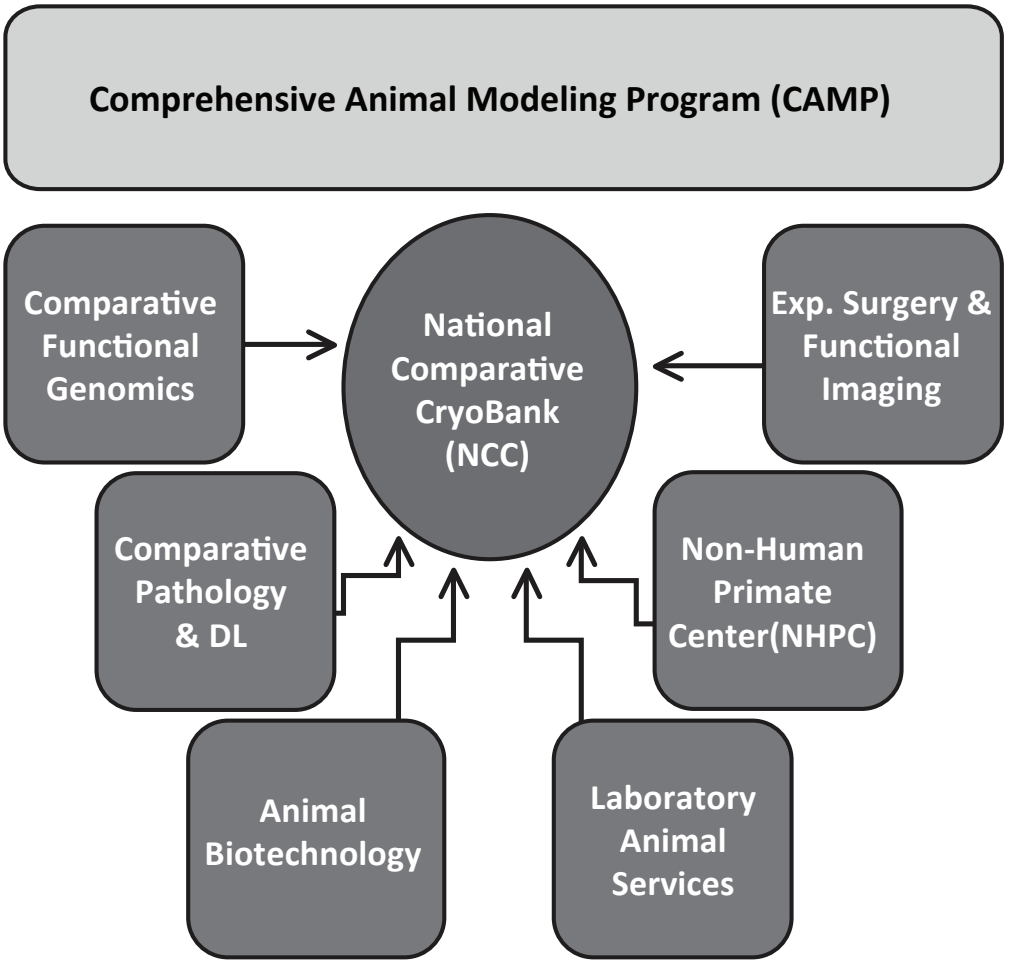
COMPARATIVE MEDICINE

COMPARATIVE MEDICINE

CHAIRMAN
Abdullah M. Assiri, DVM, PhD

ADMIN SUPPORT
Victoria Lacaocao-Vitug
Joan R. Chico

The department of comparative medicine (CMD) plays an instrumental role in the ongoing research at KFSH&RC by providing animal models and quality veterinary medical care for laboratory animals including non- human primates. The CMD offers arrays of technical and research expertise in animal modeling to address etiology and cure of animal and human diseases. The multinational CMD Staff is constituted of veterinarians, scientists, nurses and technicians. As of this year, the CMD provides and maintains close to 6000 small and large laboratory animals and supports over 45 active RAC-approved training and research projects. In addition, our genotyping and histopathology core services continued to accommodate more research projects which culminated in processing of over 2100 samples. Finally, the CMD's experimental surgery research and training programs benefited 211 participants in various surgical activities. The department will continue to move its animal modeling capabilities to meet the "omics" era demands by implementing our Comprehensive Animal Modeling Program (CAMP).


Comprehensive Animal Modeling Program (CAMP)
Comparative Functional Genomics
National Comparative CryoBank (NCC)
Exp. Surgery & Functional Imaging
Comparative Pathology & DL
Non-Human Primate Center(NHPC)
Animal Biotechnology
Laboratory Animal Services

HIGHLIGHTS

1. Development and/or provision of various animal models for human diseases.
2. Over 3,000 square meters of dedicated space for the entire department including the Primate Facility that houses Baboons (*Papio hamadryas*).
3. Expertise in veterinary medical care, anesthesia and surgery for a large variety of laboratory animals.
4. Expertise in conducting and assisting in both basic and translational research using animal models.
5. Expertise in Phenomic and genomic animal modeling.
6. A well-equipped surgical theatre with state-of-the-art surgical equipment for general, minimally-invasive and cardiovascular surgery for research and training purposes.
7. A microsurgery suite equipped with the latest state-of-the-art dissecting microscopes.

OBJECTIVES

The Department of Comparative Medicine develops and provides various animal models used in the unraveling complex human diseases that are relevant to the Saudi population. Ongoing research focuses on understanding the similarities and differences in a biological system at molecular, cellular, and organ levels in animals and humans. Our aim is to develop treatment modalities that could help in the prevention of diseases; and also to discover potential cures for human ailments.

Laboratory Animal Services (LAS)

HEAD
Falah Al Mohanna, DVM, MSc

MEMBERS
Farraj Al Samer
Abdulrahman Al Zuhaifi
Saad Al Durgham
Rolando Monzaga
Pio Oliveras
Mona Saleh
Salem Bahaa
Abdulkarim Al Enazi

KFNCCC&R HEAD
Goran Matic, DVM

MEMBERS
Ruben Delos Santos
Wilfredo Antiquera
Baltazar Caducio

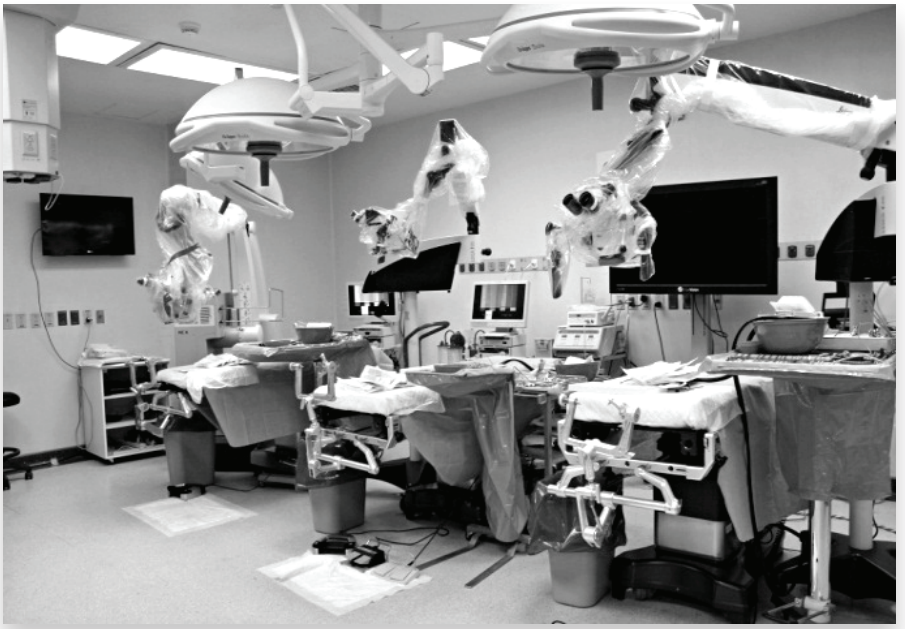
The LAS maintains quality laboratory animals and provides associated technologies for basic and translational research that is undertaken by scientists and physicians. The LAS maintains animal well-being and ensures that prudent, ethical and scientific use of animals is in accordance with both national and international guidelines. The Animal facility staffs are committed to ensure humane and ethical care and use of animals involved in approved research to advance medical, biomedical and veterinary knowledge for the benefit of scientists, investigators, physicians, students, etc.

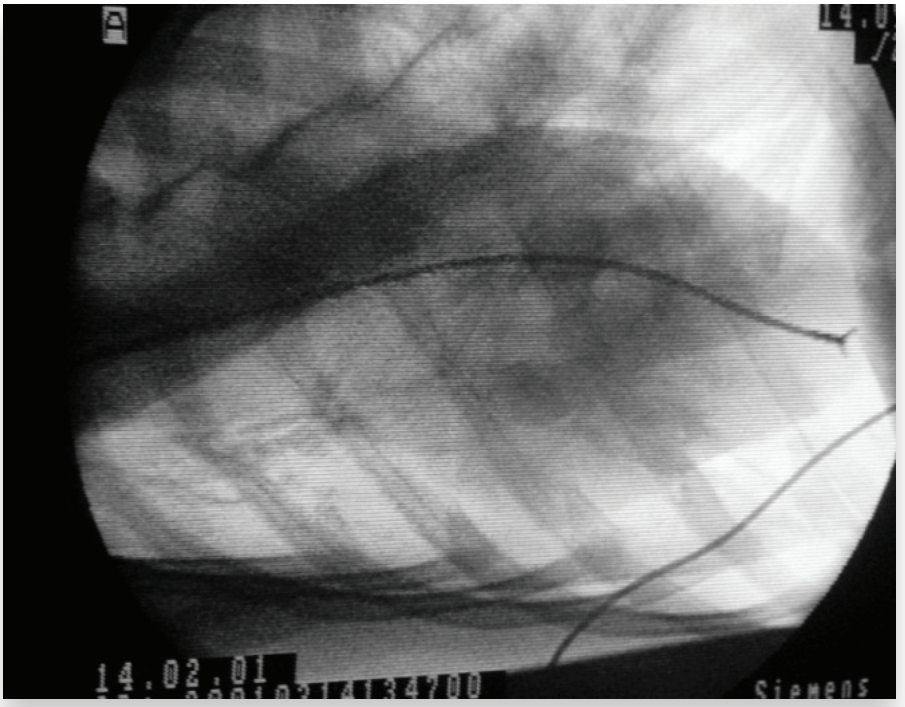
Experimental Surgery & Functional Imaging

HEAD
Ra'afat El Sayed, DVM, MVSc

MEMBERS
Farraj Al Samer
Abdulrahman Al Zuhaifi
Ludivina Apilado, BSN
Sahar Salem
Merfat Elyan
Julius Mabborang
Zohair AlHalees, MD
(Adjunct Scientist)
Essam Al-Shail, MD
(Adjunct Scientist)

State-of-the-art experimental surgical facilities that are designed to perform acute, survival surgeries and cadaver dissections for research and training purposes. This facility provides a unique opportunity for surgeons and researchers to develop and refine surgical skills and to test new innovations. The section is staffed with veterinary anesthetists, surgeons, nurses and technicians to conduct different surgical procedures.

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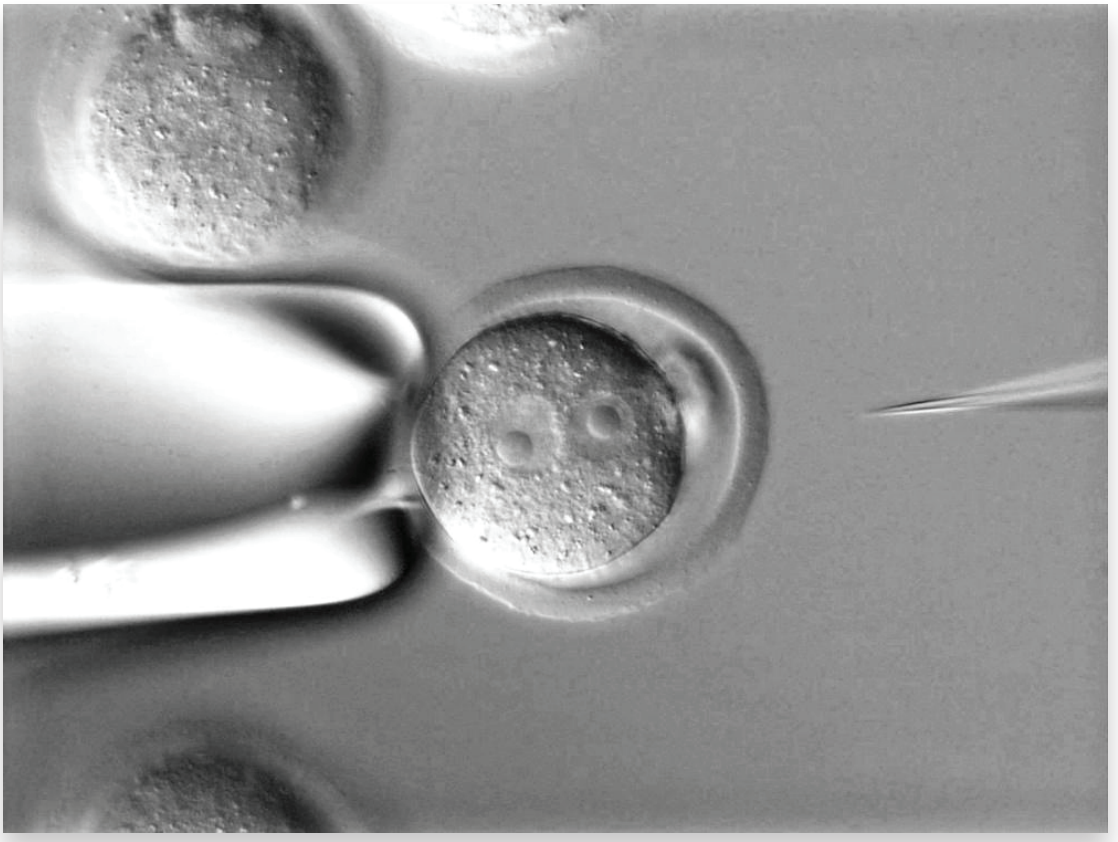
Animal Biotechnology Section

HEAD
Goran Matic, DVM

Utilizing different bio-techniques to develop novel animal models and/or produce new bio-therapeutics and diagnostic tools including animal genetic engineering, vaccines development and testing, and immunodiagnostics to improve human health. Development of national comparative cryobanking (NCC) will provide rich and accessible resources of biomedical data for Kingdom researchers.



Comparative Functional Genomics Section

HEAD
Abdullah M. Assiri, DVM, PhD

MEMBERS
Razan Abdullah
Dieter C. Broering, MD, PhD
(Adjunct Scientist)
Michael Zak DeNiro, PhD
(Adjunct Scientist)

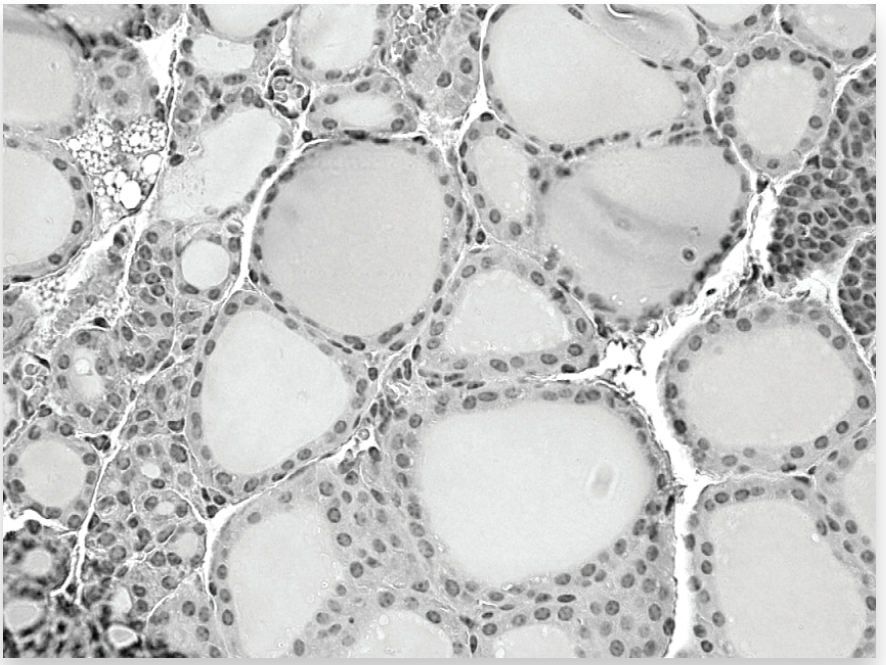
Characterizing natural or induced animal models of physiological relevancy for important health problems such as infertility, endocrine disrupters, genetics, cardiovascular diseases and diabetes. Investigating existing and emerging model organisms to address unique Saudi population diseases by adopting various phenomic and genomic tools.

Comparative Pathology & Diagnostic Laboratory

HEAD
Steve Witold Bobis, DVM

MEMBER
Hala Ahmed

To characterize pathological progress of natural 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.




RIGHT TO KNOW
CENTER
MATERIAL SAFETY DATA SHEETS
FOR
HAZARDOUS MATERIALS
USED IN THIS AREA

PUBLICATIONS OF CMD STAFF

- Al Tassan N, Khalil D, Shinwari J, Al Sharif L, Bavi P, Abduljaleel Z, Abu Dhaim N, Magrashi A, Bobis S, Ahmed H, Alahmed S, Bohlega S. A missense mutation in PIK3R5 gene in a family with ataxia and oculomotor apraxia. *Hum Mutat.* 2012 Feb;33(2):351–4. doi: 10.1002/humu.21650. Epub 2011 Dec 8. PubMed PMID: 22065524.
- Aldahmesh MA, Khan AO, Mohamed JY, Alkuraya H, Ahmed H, Bobis S, Al-Mesfer S, Alkuraya FS. Identification of ADAMTS18 as a gene mutated in Knobloch syndrome. J Med Genet. 2011 Sep;48(9):597–601. *PubMed PMID*: 21862674.
- Abu-Safieh L, Abboud EB, Alkuraya H, Shamseldin H, Al-Enzi S, Al-Abdi L, Hashem M, Colak D, Jarallah A, Ahmad H, Bobis S, Nemer G, Bitar F, Alkuraya FS. Mutation of IGFBP7 causes upregulation of BRAF/MEK/ERK pathway and familial retinal arterial macroaneurysms. Am J Hum Genet. 2011 Aug 12;89(2):313–9. PubMed PMID: 21835307; *PubMed Central PMCID*: PMC3155176.
- 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. 2011;6(7):e22244. Epub 2011 Jul 14. PubMed PMID: 21779402; *PubMed Central PMCID*: PMC3136522.

EXTRAMURAL FUNDING

This year the CMD was granted extramural funding for the research projects namely:

- RAC# 2100 012 entitled "Percutaneously Adjustable Pulmonary Band", a research collaboration between KFSH&RC and the King Abdulaziz International Medical Research Centre amounting to 1.2 million SAR.
- Two (2) KACST Project RAC# 2100 015 and 2100 016 entitled "Phenotypic and Gene Expression Profiling and their Correlation with Clinical Outcomes during the Development and Progression of Diabetic Retinopathy in Type l and II Diabetes Mellitus", a research collaboration between KFSH&RC and the King Khalid Eye Specialist Hospital amounting to 2 million SAR.

FACTS AND FIGURES

1. The Laboratory Animal Services (LAS) at KFSH&RC and KFNCCC maintains and provides research grade laboratory animals for various RAC-approved projects.

	Rats	Mice	Transgenic & Knockout Mice	Goats	Dogs	Sheep	Baboons
Used	726	2090	313	6	21	2	12
Inventory	407	1194	986	0	43	0	48
Total	1,133	3284	1299	6	64	2	60

2. The Experimental Surgery and Functional Imaging offered research and technical assistance to investigators performing different surgical research and training projects and variety of workshops and educational trainings offered to various hospital departments:

a. ACADEMIC TRAINING AND WORKSHOP

Table 1: Workshop

Activities	Date	No. of Participants (including Instructors)	Department/Section	No. of Animals Used
Thoracic Surgery	February 14, 2011	20	Surgery, Thoracic Surgery	4 Dogs
1st Pediatric Flexible Bronchoscopy Course Workshop	February 21–23, 2011	40	Pediatrics	6 Dogs
Thoracic Surgery	March 14, 2011	16	Surgery, Thoracic Surgery	4 Dogs
Intensive Microsurgery Hands-On Course (3 series of workshops/ 5 days per workshop)	May 8–11, 2011 Sept. 24–28, 2011 Dec. 17–21, 2011	15	Neurosciences	115 Rats
WFNS Skull Base Surgery Workshop: A Hands-on Cadaver Dissection Course	Nov. 21–23, 2011	35	Neurosciences	10 Cadaver Heads
Residents' Anastomosis & Vascular Surgery Workshop Dry Lab & Live Training	Nov. 24, 2011	25	Surgery	3 Dogs
Advanced Laparacoscopic Hands-on Course	Dec. 7–8, 2011	17	Urology	6 Goats
TOTAL		**168**		**138 Animals** **10 Cadaver Heads**

b. TRAINING PROGRAMS

Table 2: Hands-On Surgical Training

Activities	Date	No. of Participants	Department/Section	No. of Animals Used
Hands-On Surgical Training	Feb.7,13 & 27, 2011	9	Surgery	3 Dogs
	March 1, 7, 13, 23 & 27, 2011	15	Surgery	5 Dogs
	September 13, 18, 20, 25 & 27, 2011	10	Surgery	5 Dogs
TOTAL		**34**		**13 Dogs**

Table 3: Microsurgery Weekly Training Program

Activities	RAC #/Department	Principal Investigator	No. of Participants
Hands-On Microsurgical Training	RAC# 2080 003 Liver Transplantation	Prof. Dr. Mohammed Al Sebayel	1
	RAC # 2112 002 Plastic Surgery	Dr. Ali Al-Malaq	4
	Orthopedic Surgery	Dr. Nezar Hamdi	4
TOTAL			**9**

Table 4: Training Program Participants

Level of Study	No. of Male	No. of Female	Program	Training Period
*PhD Program		1 from KSU	RC Training & Education	On-going
Medical Students	3 (2 KSU & 1 Dammam)	4 from KSU	Al-Razi Program	For 4 weeks July 16–August 10, 2011
Ibn Sena Program	13		King Abdulaziz & His Companion Foundation for the Gifted	For 3 weeks July 2–20, 2011
TOTAL	**16 Males**	**5 Females**		

3. The Comparative Functional Genomics Section performed strains' genotyping for the following investigators to insure line maintenance and experimental crossings.

PI Name	Name of mouse strain	No. of genotyped samples
Fowzan Alkuraya	CARF	195
Fowzan Alkuraya	WSS	336
Coralie Poizat	BALb/c	72
Michael DeNiro	AKITA	10
Total		**613**

4. Comparative Pathology and Diagnostic Laboratory for different RAC projects which include paraffin embedding and sectioning, staining and blood & frozen samples processing.

PI Name	RAC#/ Others	Paraffin Specimen	Parrafin Section	Frozen Specimen	Frozen Section	Staining	Blood	Total
Falah AlMohanna	Students	48	96			96		96
Yufei Shi	2050 048	63	134			71		
Futwan AlMohanna	2011 011	6						12
Fowzan AlKuraya		23	460	17	300	6		766
Salma Wakeel	2020 023	6	12					12
Imad Naja		9	18			9		18
Abbas Hawwari	2080 046	8						8
Mai AlMohanna	2110 019			278			195	473
TOTAL								**1,519**

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. The Heart Centre
16. The Organ Transplant Centre

NATIONAL COLLABORATIONS

1. King Saud University
2. King Faisal University
3. King Abdullah International Medical Research Centre
4. Security Forces Hospital
5. King Fahad Medical City
6. Military Hospital
7. AlFaisal University
8. Taibah University
9. King Khalid University

INTERNATIONAL COLLABORATIONS

1. Emergent Bio-Solutions
2. University of Leuven, Belgium
3. John Hopkins
4. University of Pittsburg
5. Washington State University

LIST OF RAC APPROVED PROJECTS

1.	RAC#2110 025	Anti-Tumor Activity of XIAP Inhibitor Embelin on Mice Xenografts of Epithelial Carcinomas
2.	RAC# 2110 021	The Molecular Characterization of the Mechanism in BRAF Splicing Variants and Pseudogene Mediated Signaling & Thyroid Turmogenesis in Transgenic Mice
3.	RAC# 2110 011	The Use of Rat Embryonic Stem Cells in Decellularized Rat Hearts
4.	RAC# 2110 010	Acceptability of Experimental N-Methyl D-Aspartame (NMDA) Receptor Antagonist CGP39551 as an Orally Competitive Glutamate & Aspartate Receptor Blocker in Rodents
5.	RAC# 2100 024	Epigenetic Regulation by Nuclear Calcium in the Heart
6.	RAC# 2100 023	Role of LMPTP in Cardiovascular Diseases
7.	RAC# 2100 016	Phenotypic Anchoring, Global Gene Expression Profiling & Correlative Clinical Outcome during the Development & Progression of Diabetic Retinopathy in Type II Diabetes Mellitus
8.	RAC# 2100 012	Percutaneously Adjustable Pulmonary Artery Band
9.	RAC# 2100 006	Making & Characterization of the Mouse Model for Hypogonadism, Alopecia, Diabetes Mellitus, Mental Retardation & Extrapyramidal Syndrome
10.	RAC# 2100 003	Radiolabeled Bioactive Peptides: Potential Molecular Targeting Radiopharmaceuticals for Cancer Imaging & Therapy

11.	RAC# 2092 001	Rodent Acute Animal Model for Organ Xenotransplantation: Microvascular Surgical Training
12.	RAC# 2090 028	Role of Excitatory Amino Acids in Trans-fat-induced Obesity, Dyslipidemia, Hepatic Steatosis & Cognitive Impairment
13.	RAC# 2090 014	Development of F18-labeled Radiopharmaceuticals (beyond [18F] FDG) for Use in Oncology & Neurosciences
14.	RAC# 2082 001	Microvascular Techniques in Surgery for Infertility & Erectile Dysfunction: Training of the Urology Staff
15.	RAC# 2080 052	Proteomic Analysis, Anti-Resorptive Properties & Tumor Cell Cytotoxicity
16.	RAC# 2080 046	RORγt Role in T Cell Development, Autoimmunity & Transformation
17.	RAC# 2080 044	Study of Photodynamic Therapy on Nude Mice using Different Tumors and Photosensitive Drugs
18.	RAC# 2080 040	Development of Human Embryonic Stem Cells (hESCs) Lines from Discarded IVF Laboratory Embryos & Mouse Embryonic Stem Cells (mESCs) for the Treatment of Genetic Metabolic Disorders: A Major Cause of Disability in Children
19.	RAC# 2080 031	Role of C-MET in Saudi Arabian Papillary Thyroid Carcinoma for Novel Therapy
20.	RAC# 2080 030	Prognostic Significance of Genetic Alterations in Saudi Colorectal Cancers
21.	RAC# 2080 029	Cyclooxygenases: Target for Epithelial Ovarian Cancer Prevention & Treatment
22.	RAC# 2080 027	Study of the Anti-Cancer Properties of PAC (A Novel Curcumin Analogue) In Vitro & In Vivo
23.	RAC# 2080 019	Transcriptional Regulation of TCR
24.	RAC# 2050 048	Investigation of BRAF Mutation in Thyroid Carcinoma from Saudi Population
25.	RAC# 2100 013	The Anti Breast Cancer Potential of Eugenol. (Abdelilah Aboussekhra)
26.	RAC# 2110 002	Development of Ga-68 Based PET- Radiopharmaceuticals for Management of Cancer and other Chronic Diseases. (Ibrahim Al Jammaz)
27.	RAC# 2112 002	Microsurgery Training. (Ali Al Malaq)
28.	RAC# 2022 008	Microsurgery Intensive Hands-On Course. (Essam Al-Shail)
29.	RAC# 2100 015	Phenotypic Anchoring, Global Gene Expression Profiling, and Correlative Clinical Outcome During the Development and Progression of Diabetic retinopathy in Type II Diabetes Mellitus. (Michael Deniro).
30.	RAC# 2080 009	Investigation of the Role of Stromal Fibroblasts in the Development of Breast Carcinoma. (Abdelilah Aboussekhra).
31.	RAC# 2080 023	Identification and Therapeutic Targeting of ABCB5+ Tumor Stem Cells. (Chaker Adra).
32.	RAC# 2080 022	Penile Autotransplantation in the Rat: Impact of Microsurgical Anastomosis of the Dorsal Neurovascular Bundle. (Raouf Seyam).
33.	RAC# 2060 007	Metabolic Syndrome, Diabetes and Cognitive Decline: Effect of Dietary Components on Insulin Resistance, Hyperlipidemia, Inflammation and Cognition in a Rodent Model. (Katherine Collison).
34.	RAC# 2060 016	Investigating the Role of the Actin-Bundling Protein (Fascin) in Regulating Dendritic Cells Migration and Breast Cancer Metastasis in Saudi Population. (Monther Al Alwan).

35.	RAC# 2110 019	The Effect of Selenium and Lycopene on Quidative Stress in Bone Tissue and Some Indicators of Its Metabolism in Rats Exposure to Cadmium. (Mai Al Mohanna).
36.	RAC# 2082 003	Microsurgery Training. (Mohammed Al Sebayel).
37.	RAC# 2112 001	Laparoscopic Hands on Workshops. (Hassan Al Zahrani).
38.	RAC# 2032 002	Training of Surgical Residents in Bowel Anastomosis. (Luai Ashari).
39.	RAC# 2031 086	Optimization of Tunica Albginea Free Graft for Corporoplastty: an Experimental Animal Study. (Raouf Seyam).
40.	RAC# 2050 032	The Effect of Alpha Adrenergic Blockers on the Ureter: An in Vivo Study in the Dog. (Waleed Al Taweel).
41.	RAC# 2102 001	Pediatric Flexible Bronchoscopy Course. (Sami Alhaider).
42.	RAC# 2090 020	A Novel Retractor for Laparoscopic Urologic Procedures: An acute Study in Dogs. (Raouf Seyam).

FUTURE PLANS

1. Launching Comprehensive Clinical Pathology Laboratory
2. Establishing of National Comparative Cryobank (NCC)
3. Improving the CMD Comprehensive Animal Modeling Program (CAMP)
4. Providing non-traditional animal models such Zebrafish, Xenopus laevis, etc
5. Establishment of the Kingdom's first Non-Human Primate Center (NHPC)
6. Establishment of robotic surgery capabilities for research and training
7. Obtaining international certification and accreditation

CYCLOTRON AND RADIOPHARMACEUTICALS

CYCLOTRON AND RADIOPHARMACEUTICALS

CHAIRMAN
Manhar M. Vora, PhD

DEPUTY CHAIRMAN
Ibrahim Al-Jammaz, PhD

ADMIN SUPPORT
Nora B. D'Souza
Jhonna L. Canicosa
Cathelyn Guerra

Year 2011 was a remarkable year for cyclotron and Radiopharmaceuticals Department, as the Cyclotron Expansion project was successfully completed after several years of planning. The ambitious project began in year 2007 with the building design, equipment selection, tendering, followed by construction of the specialized building for housing the cyclotron and radiopharmaceuticals manufacturing equipment, and ending with commissioning and validations for the intended applications.

The unique program of radiopharmaceuticals manufacturing that began in year 1982 has now come a full circle with replacement of the aged cyclotron with a state-of-the-art machine, and practically mirror-imaging the old facility in the new building. Furthermore, the new facility is equipped with additional machinery that will allow manufacturing of additional radiopharmaceutical products fulfilling the goal of making the Kingdom self-sufficient in over 90% of its radiopharmaceutical needs for diagnostic imaging.

Cyclotron and Radiopharmaceuticals Department performs two distinct functions in the Research Centre: Radiopharmaceuticals manufacturing; and Radiotracer Research.

RADIOPHARMACEUTICAL MANUFACTURING: Radiopharmaceuticals are the pharmaceutical products that are labeled with radioactive isotopes, and are the key ingredients in practice of nuclear medicine, either for diagnostic imaging or for therapy. C&R Department is the only facility of this kind within the geographical region manufacturing these specialty products. Of special interest are the radiopharmaceuticals labeled with positron emitting radionuclides as integral components of the most contemporary imaging modality of Positron emission tomography (PET).

Working towards the ultimate goal of comprehensive manufacturing facility, several new products are added at regular intervals. As a result, some 40 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.

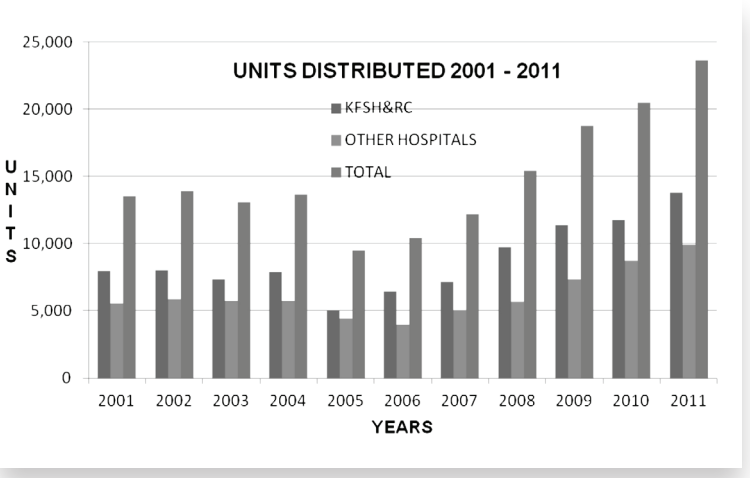
RADIOTRACER RESEARCH: Radiotracers are the tools for probing at molecular level the biochemical and physiological processes. A well designed molecule labeled with an appropriate radioisotope has the potential to probe specific biological systems *in vivo* with minimum perturbation of the whole organism. 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. Active research projects culminated into several publications and presentations at international conferences.

ACCOMPLISHMENTS YEAR 2012

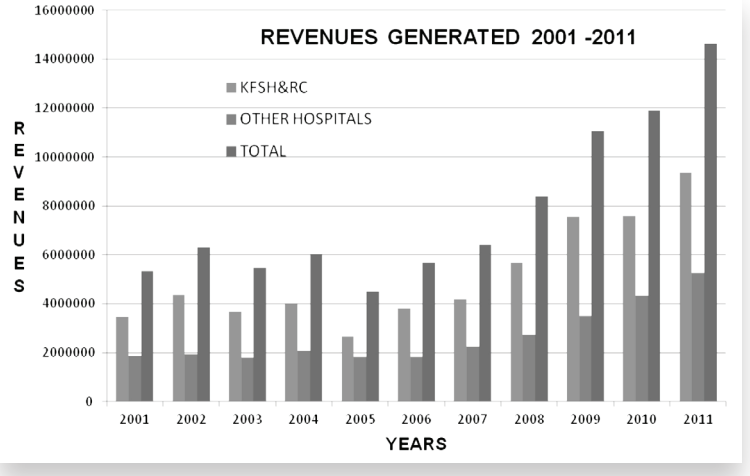
- RADIOPHARMACEUTICAL MANUFACTURING: Kingdom-wide distribution of radiopharmaceuticals continued at the usual pace with improvement in reliability as the new equipment came into use. Also, the trend of increase in products distribution continued in the year 2012, with 15% increase in distribution of the PET radiopharmaceutical, FDG. Corresponding revenue increased by 22%.
- 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.
- RADIOTRACER RESEARCH: The small research group continued to perform radiotracer development, generate new research proposal and the extramural research funds and to publish research results in peer reviewed journals.
- RADIOPHARMACEUTICALS PRODUCTION RELATED:
  - 23693 units of radiopharmaceuticals distribution to 40 nuclear imaging centers in the Kingdom and abroad
  - SR14,624,564 revenues generated from distribution of radiopharmaceuticals
  - >99% process success rate in manufacturing radiopharmaceutical products
  - Achieved objectives of the ISO 9001:2008 Quality Management System, including customer satisfaction rate of 95.6%
  - Re-certification of ISO 9001:2008 Quality Management recertification
  - International Atomic Energy Agency (IAEA): A senior staff member co-authored a book: Cyclotron Produced Radionuclides: Guidance on Facility Design and Production of FDG
  - International Atomic Energy Agency (IAEA); participation in four research projects:

- ◊ Radiotracers beyond FDG
- ◊ Developing Ga-68 radiopharmaceuticals
- ◊ Radiotracers labeled with Cu-64 and I-124 radionuclides
- ◊ Radiotracers labeled with Y-90 and Lu-177 radionuclides

- ■ RADIOTRACER RESEARCH RELATED:
  - □ 10 active research projects
  - □ >5 million Grant funds (KACST funded, over 3–4 years)
  - □ 8 publications in peer-reviewed journals
  - □ 6 abstracts and presentations



Total Number of Units Distributed (2001–2011)



Total Revenues Generated (2001–2011)

MOLECULAR ONCOLOGY

MOLECULAR ONCOLOGY

CHAIRMAN
Peter A. Hall, MD, PhD, FRCPath

ADMIN SUPPORT
Miss Robyn Seamer

The purpose of this newly established department is to enhance our 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 in the Saudi population. Central to our purpose is interaction with other groups and Departments within the Institution and the development of meaningful national and international collaborations. There are five sections within the Department, (1) Breast Cancer, (2) Cancer Biology & Experimental Therapeutics, (3) Molecular Endocrinology, (4) Septin Biology and (5) Translational Cancer Research.

Breast Cancer Research

HEAD
Suad Bint Mohamed Bin Amer, PhD

MEMBER
Asmaa Nofal, BSc, *Research Technician*

Breast cancer is the major cause of morbidity and mortality among females in Saudi Arabia. Clinical observations indicate that the breast cancer developed before the age 45 accounts for 45% of all female breast cancers in Saudi Arabia as compared to 9.6% in USA. Breast cancer in young Saudi females is more aggressive in nature with poor prognosis and disease free survival. Thus new diagnostics, 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 preinvasive 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 course of breast cancer progression.

RESEARCH PROJECTS

PROJECT TITLE: **Identification of environmental and genetic factors that influence breast cancer development and therapy in Saudi females**

RAC # 2031 091. In collaboration with KACST.

INVESTIGATORS: *Suad M Bin Amer, Dilek Colak, Taher Al –Tuweigeri, Asma Tulbah, Dahish Ajarim and Osama Almali.*

PROJECT DESCRIPTION: We aim to establish the consensus gene profile for Saudi population by using Micro Array technique well as to study the role of tissue micro environment and architecture in the process of tumor development and progression by comparing the gene profiles of breast tumors with tumor adjacent tissues. We are also interested to know that if the different molecular subtypes of breast cancer also respond differently to preoperative chemotherapy. It has already been indicated that the different molecular classes of breast cancer show distinct sensitivities to preoperative chemotherapy, whereby basal-like and ErbB2+ subtypes of breast cancer are more sensitive to Paclitaxel and Doxorubicin containing preoperative chemotherapy than the luminal and normal-like cancers.

Given the facts that the patients in KSA normally present themselves to clinicians at a young age and more aggressive stage of breast cancer, we are aim to study the potential that chemotherapy responses, specifically resistance may differ significantly between the Caucasians and Middle Eastern populations. The Affymetrix Genechip Human Genome U133 Plus 2.0 Array is being used to carry out the gene expression studies.

PROJECT PROGRESS: Specimen collection: Freshly resected Breast tumor and tumor adjacent tissues samples were collected and handled in collaboration with clinicians and pathologists by using the internationally standardized protocol. Clinicopathological profile data was obtained about tumor subtype (WHO classification), histological grade, lymphovascular invasion, margins status, number of involved lymph nodes, and the presence of extracapsular invasion before using the tissue for experiments.

Genome-wide Gene Expression Analysis: We performed genome-wide gene expression profiling to characterize the underlying biological mechanisms of breast cancer in young women in Saudi Arabia. We analyzed the whole-genome mRNA expression profile from tumor and adjacent disease free tissues of 115 samples using Affymetrix GeneChip Human Genome U133 Plus 2.0 Arrays. We compared mRNA expression in tumors in young (≤45 years) (n=35) to those arising in two mature groups: 45 to 55 (n=13); and older age ≥55 (n=25). Within the young women's subset, additional analyses were performed comparing women age younger than 35 years (very young) with those age 35 to 45 years. Functional pathway, gene ontology and network analysis of tumor specific genes (up/down-regulated) were performed. Moreover, we also compared the gene expression profile characteristic of the sequential disease stages (DCIS and IDC) of breast cancer as well as age-matched normal controls within the young patients to discover genes specifically activated or inactivated during the course of breast cancer progression.

MAJOR FINDINGS FOR THIS YEAR

1. We have identified 77 signature genes specific to tumor in young age (≤ 45). A subset of differentially expressed genes was validated using real-time RT-PCR. In addition, selected signature genes were also confirmed by using immunohistochemical staining for young group vs. older group peri-menopause and post-menopause of Saudi breast cancer patients.
   The enriched functional categories of young-age tumor signature genes include carcinogenesis, tissue development, cellular development, cellular growth and proliferation, tumor morphology, and cell death.
2. Furthermore, we found that 143 genes differentially regulated between IDC and DCIS, 96% of which were down-regulated in IDC compared to DCIS. The network analysis revealed potential

critical regulatory role of PI3K/Akt, NFκB, Jnk, and ERK pathways significantly alterd between DCIS and IDC in younger women.

3. DCIS to IDC progression potential markers: Ductal carcinoma *in situ* (DCIS) is heterogeneous group of preinvasive tumors which may progress rapidly or slowly to invasive cancer. Therefore, an ability to identify which DCIS lesions are likely to progress to potentially lethal stage invasive ductal carcinoma (IDC) would greatly help the treatment plan and the disease prognosis.

   To identify the putative genes involved in disease progression in young women, we performed genome-wide gene expression profiles characteristic of the sequential disease stages (DCIS and IDC) of breast cancer and compared to age-matched normal controls in young women (≤45 years). We defined the potential progression genes, or genes that are potentially involved in the earliest molecular step in acquiring the capacity to invasion are those that are significantly altered in both DCIS and IDC stages. We identified 1015 and 4873 genes differentially expressed (up/down-regulated) in DCIS and IDC compared to normal, respectively, and 697 probes (corresponding to 484 unique genes) had significantly altered expression in both DCIS and IDC.

   We next performed cross-species comparative genomics analysis to identify potential gene marker for DCIS progression to IDC that are conserved in mouse and human. The comparison of our progression signature genes with the murine markers of progression (human orthologous) revealed 16 unique genes that were conserved between mouse and human ($p < 0.001$). All of these genes are highly expressed in both DCIS and IDC compared to age-matched normal controls. Gene ontology (GO) analysis revealed that these genes are mainly involved in biological processes including mitosis, cell cycle, embryonic development, DNA replication, growth and apoptosis.

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

RAC # 2110 016. In collaboration with Al faisal University).

INVESTIGATORS: *Suad Bint Mohamed Bin Amer, Ahmed Yaqinuddin, Dilek Colak, Taher Al –Tuweigeri, Asma Tulbah, Dahish Ajarim and Osama Almalik.*

PROJECT DESCRIPTION: Breast Cancer remains one of the commonest cancers affecting women worldwide. To date several genetic, epigenetic (e.g. DNA methylation), as well as proteinaceous biomarkers have been found to be associated with the disease but their utility as robust indicators of disease remains uncertain. In light of this, there is a need to identify robust, specific as well as sensitive biomarkers that will be useful for detecting breast cancers and differentiate between aggressive vs non-aggressive tumors. Micro-RNAs (miRs) are small 18–24 nucleotide RNAs which regulate the expression of approximately 30% of human genes and whose expression is frequently dysregulated in cancers. Contributions from a number of laboratories have demonstrated that different cancers are associated with distinct miR profiles. Recently, miRs have been found in significantly large copy numbers in 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 prolong 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 that are breast cancer-specific and which can therefore be employed as disease predicting biomarkers. Towards that end, we propose to carry out the following two specific aims.

1. Identify Breast cancer-specific miRs by comparing miR profiles derived from serum samples of breast cancer patients to those from healthy control individuals.
2. Evaluate usefulness of identified miRs as reliable biomarkers for early diagnosis and for progression of disease.

PROJECT PROGRESS: Samples: 10 ml of blood is obtained from 200 patients with breast cancer after obtaining appropriate informed consent according to the guidelines detailed by the Ethical Review Committee and 50 controls (we use blood donor consent for research use for sample for controls). Serum is separated from these samples and is stored at -80°C until used.

Cancer Biology & Experimental Therapeutics

HEAD
Abdelilah Aboussekhra, PhD

MEMBERS
Mai Al-Mohanna, PhD, *Scientist*
Nisreen Al-Moghrabi, PhD, *Scientist*
Bedri Karakas, Ph.D, Associate *Scientist*
Mysoon Al-Ansari, PhD, *Postdoctoral Fellow (Grant Employee)*
Huda Al-Khalaf, PhD *(Adjunct Scientist)*
Ibtehag Al-Sharif, BSc, *Research Assistant*
Nujoud Al-Yousef, BSc, *Research Assistant*
Siti Hendrayani, MSc, *Research Assistant (Grant Employee)*

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.

MAJOR FINDINGS FOR THIS YEAR

1. The tumor suppressor p16^{INK4A} protein is also a major modulator of gene expression.
2. Caffeine up-regulates p16 and p53 and suppresses breast carcinoma-stroma cross-talk.
3. Role of TRKC, CTNNB1 and STK15 in the response of medulloblastoma cells to vincristine and lomustine.
4. Camel urine has anti-cancer properties *in vitro*

RESEARCH PROJECTS

PROJECT TITLE: **Investigation of the role of stromal fibroblasts in the development of breast carcinoma: The tumor suppressor p16^{INK4A} protein as target**

RAC # 2080 009. Supported by KACST.

INVESTIGATORS: *A. Aboussekhra (PI), Mysoon Al-Ansari and Siti-Faujiah Hendrayani*

PROJECT DESCRIPTION: In the present proposal we are aiming at elucidating the functional interplay between stromal fibroblasts and breast carcinoma. More precisely we will study the role of the tumor suppressor p16 in the stromal-tumor interaction. To this end we are planning to investigate p16 expression level in Carcinomas-Associated Fibroblasts (CAFs) and their corresponding Tumor Counterparts Fibroblasts (TCFs) from the same patient. Furthermore, we are also planning to study the effect of p16 down-regulation, using p16 siRNA, on the molecular and cellular features of breast stromal fibroblast cells and on the proliferation of breast carcinomas. The resulting data will provide new insights into the importance of breast stromal fibroblasts in the development and treatment of carcinomas and the active involvement of p16 in this complex phenomenon.

PROGRESS: p16 knock-out in mice embryonic fibroblasts enhanced angiogenesis in human breast cancer in mice. Furthermore, p16-deficient cells enhanced the aggressivity and behavior of cancer cells by increasing the expression of various oncoproteins in a paracrine fashion

Additionally, we have demonstrated that low concentration of caffeine inhibits the procarcinogenic effect of breast stromal fibroblasts, through suppressing the expression and secretion of various cancer-prone molecules, such as IL-6, MMP2 and SDF1. This effect is mediated through the up-regulation of p53, wich is a negative regulator of these proteins.

Using microarray analysis and specific knock-down of p16 using shRNA, we have shown that this tumor suppressor gene controls the expression of more than 2000 genes, involved in different cellular metabolisms, including DNA repair, senescence, angiogenesis and cell proliferation (Figure 1).

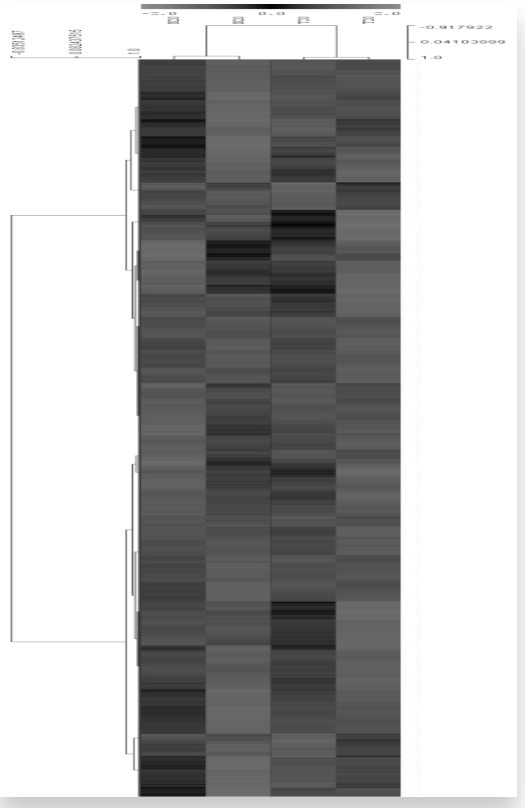


Figure 1. Hierachical clustering of differentially expressed genes between cells expressing either control shRNA or p16 specific shRNA.

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

RAC # 2080 027

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 rats.

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, which will allow us, in the near future, to use this agent in phase 1 clinical trial in order to prove its safety and efficiency in humans.

PROGRESS: We have recently using different breast cancer cell lines that PAC is more efficient against basal like than luminal breast cancer cells, and its effect is p53-dependent.

Furthermore, we have shown that PAC suppresses the expression and secretion of IL-6 from breast cancer cells. This effect is mediated through the JAK2/STAT3 pathway.

Conclusion: PAC could constitute a powerful, yet not toxic, new chemotherapeutic agent against basal like type of breast cancer.

PROJECT TITLE: **Study the potential anti-cancer properties of camel urine**

RAC # 2100 018

INVESTIGATORS: *A. Aboussekhra (PI), Nujoud Al-Yousef, Khaled Al-Hussein, Ibrahim Al-Jammaz, Ameera Gaafar and Basem Al-Otaibi*

PROJECT DESCRIPTION: Our major aim is study the potential anti-cancer effect of camel urine (CU) against various cancer cell lines both *in vitro* and *in vivo*.

PROGRESS: We have demonstrated that different samples of CU do not affect normal cells, while they trigger apoptosis in various cancer cells through the intrinsic pathway via Bcl-2 decrease and inhibits cell proliferation (Figure 2). Moreover, CU is not cytotoxic against peripheral blood mononuclear cells and has strong immuno-inducer activity through inducing IFN-γ and inhibiting the Th2 cytokines IL-4, IL-6 and IL-10. Furthermore, CU down-regulates the cancer-promoting proteins survivin, β-catenin and cyclin D1 and increases the level of the cyclin-dependent kinase inhibitor p21.

CONCLUSION: CU has specific and efficient anti-cancer and potent immune-modulator properties *in vitro*.

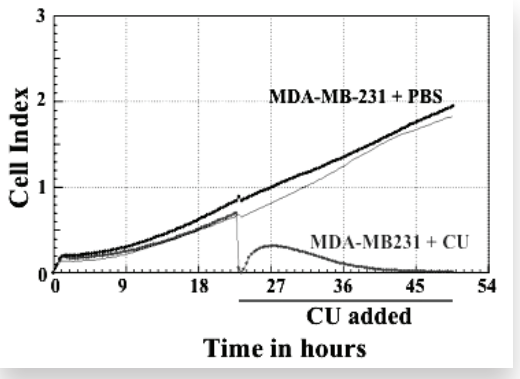


Figure 2. Camel urine inhibits cell proliferation of breast cancer cells. Sub-confluent MDA-MB231 cells were either sham-treated or challenged with CU (16 mg/mL) for the indicated periods of time and cell proliferation rate was determined using the Real-Time Cell Electronic Sensing System.

FUTURE RESEARCH DIRECTION

Further elucidate the molecular mechanisms that govern the functional interplay between breast carcinomas and their adjacent stromal fibroblasts and the role of the tumor suppressor p16 and the cytokine IL-6 in this interaction. We are also interested in further studying the potential role of BRCA1 methylation in predisposition and early onset of breast cancer in the Saudi females. Furthermore, we would like to further characterize the anti-cancer effects of PAC and camel urine *in vivo* in animal models.

PUBLICATIONS

- Abeer J. Al-Qasem, Mohamed Toulimat, Abdelmoneim M. Eldali, Asma Tulbah, Nujoud Al-yousef, Sooad K. Al-Daihan, Nada Al-Tassan, Taher Al-Tweigeri and Abdelilah Aboussekhra. TP53 genetic alterations in the Arab breast cancer patients: Novel mutations, pattern and distribution. (2011) *Oncology Letters* 2: 363–369.
- Al-Khalaf HH, Hendrayani SF, Aboussekhra A. The Atr protein kinase controls UV-dependent up-regulation of $p16^{INK4A}$ through inhibition of Skp2-related polyubiquitination/degradation. (2011) *Mol Cancer Res.* 9: 311–319.
- Al-Khalaf HH, Colak D, Al-Saif M, Al-Bakheet A, Hendrayani SF, Al-Yousef N, Kaya N, Khabar KS, Aboussekhra A. p16 Positively Regulates Cyclin D1 and E2F1 through Negative Control of AUF1. (2011) *PLoS One* 6(7):e21111.
- Al-Hujaily EM, Mohamed AG, Al-Sharif I, Youssef KM, Manogaran PS, Al-Otaibi B, Al-Haza'a A, Al-Jammaz I, Al-Hussein K, Aboussekhra A. PAC, a novel curcumin analogue, has anti-breast cancer properties with higher efficiency on ER-negative c cells. (2011) *Breast Cancer Res. & Treat.* 128: 97–107.
- Shinwari Z, Al-Hindi H, Al-Shail E, Khafaga Y, Al-Kofide A, El-Kum N, Aboussekhra A. Response of Medulloblastoma Cells to Vincristine and Lomustine: Role of TRKC, CTNNB1 and STK15. (2011) *Anticancer Res.* 31(5):1721–33.
- Al-Moghrabi N, Al-Qasem AJ, Aboussekhra A. Methylation-related mutations in the BRCA1 promoter in peripheral blood cells from cancer-free women. (2011) *Int J Oncol.* 39(1):129–35.
- Aboussekhra A. Role of cancer-associated fibroblasts in breast cancer development and prognosis. (2011) *Int. J. Dev. Biol*; 55, 841–849.

Molecular Endocrinology

HEAD
Ali Al-Zahrani, MD, PhD

The molecular endocrinology unit has just been established. We are currently in the process of getting the essential equipment, staffing, etc. The Molecular Endocrinology Unit focuses on two main areas. The first is translational research on endocrine neoplasms, relating the phenotypes with genotypes. Our aim is to define the molecular basis of the variations these tumors show in their presentations, response to therapy and prognosis. We are also planning to study some of the signal transduction pathways involved in the pathogenesis of these tumors such as the MAP Kinase and the PI3K-AKT pathways. The second aspect of our work is to study genetic abnormalities in a number of hereditary endocrine diseases such as thyroid hormone resistance syndromes, congenital hypothyroidism and others.

RECENT PUBLICATIONS

- Alzahrani AS, Zou M, Baitei EY, Parhar RS, Al-Kahtani N, Raef H, et al. Molecular characterization of a novel p.R118C mutation in the insulin receptor gene from patients with severe insulin resistance. *Clin Endocrinol* (Oxf). 2012;76(4):540–7.
- Alzahrani AS, Ceresini G, Aldasouqi SA. "The Role of Ultrasonography in the Differential Diagnosis of Thyrotoxicosis: A Non-invasive, Cost-effective, and Widely available but Under-utilized Diagnostic Tool". *Endocr Pract*. 2012:1–35.
- Alzahrani AS, AlShaikh O, Tuli M, Al-Sugair A, Alamawi R, Al-Rasheed MM. Diagnostic value of recombinant human thyrotropin-stimulated (1)(2)(3)I whole-body scintigraphy in the follow-up of patients with differentiated thyroid cancer. *Clin Nucl Med*. 2012;37(3):229–34.
- Alzahrani AS, Alqaraawi A, Al-Suhaibani F, Al Mana H, Abalkhail H. Pancreatic metastasis arising from a a BRAFV600E-positive papillary thyroid cancer: the role of endoscopic ultrasound-guided biopsy and response to sorafenib therapy. *Thyroid*. 2012.
- Zou M, Baitei EY, Alzahrani AS, Parhar RS, Al-Mohanna FA, Meyer BF, et al. Mutation prediction by PolyPhen or functional assay, a detailed comparison of CYP27B1 missense mutations. *Endocrine*. 2011;40(1):14–20.
- Alshaikh OM, Almanea H, Alzahrani AS. Paget disease of the bone: does it exist in Saudi Arabia? *Ann Saudi Med*. 2011;31(3):305–10. PMCID: 3119975.

Septin Biology

HEAD
Peter Hall, MD, PhD, FRCPath

FUTURE MEMBERS
Hilary Russell, BSc, PhD, MA, Res, Eth
Aduct Principal Scientist
Mysoon Al-Ansari, PhD *Adjunct Scientist*

The septins are a family of evolutionarily conserved genes[1] that encode GTP and GDP binding proteins capable of forming non-polar filamentous structures with diverse cellular roles. Many of these roles focus on membrane events associated with cell polarity determination and cellular morphogenesis[2].

Our interest in this complex group of genes began with the discovery by Dr Hilary Russell of what is now known as *SEPT9* and the observation of complex splicing events. A number of studies from our laboratory have shown perturbed expression of *SEPT9*, and other septins, in disease states and in particular in neoplasia.

A striking observation is the generation of a particular truncated *SEPT9* isoform (*SEPT9_i4*) by two distinct transcripts known as *SEPT9_i4* and *SEPT9_i4** and perturbation of the ratio of these transcripts in cancer. This isoform has interesting properties and can disrupt septin-containing filaments, and recent data indicate it can have profound effects on microtubule dynamics[3]. The phenomenon of there being more than one transcript to encode some septin isoforms is seen in other human septin genes and deserves explanation.

A number of studies have addressed the physiology of *SEPT9_i4* and *SEPT9_i4** transcripts and we have shown that there are marked differences in the regulation of expression of these transcripts and their translation into *SEPT9_i4* protein[4]. We are extending these studies in current work and addressing the physiological and pathological significance of the other splicing events in *SEPT9*. In other studies we have been defining the genomics, expression and regulation of other septin genes and in particular *SEPT6* and have compelling data on the perturbation of *SEPT6* in disease. Septin interacting proteins such as anillin are also areas of interest for our group.

Our current work is focused on cataloging the details of septin transcripts in human tissues both in physiological and pathological states and parallel molecular and cell biological studies of the properties of septin transcripts and isoforms with the goal of understanding their regulation and function.

References:

1. Russell SE, Hall PA. Septin genomics: a road less travelled. *Biol Chem*. 2011; 392:763–7.
2. Hall PA, Russell SE. Mammalian septins: dynamic heteromers with roles in cellular morphogenesis and compartmentalization. *J Pathol*. 2012;226:287–99.
3. Chacko AD, McDade SS, Church S, Kennedy R, Price J, Hall PA, Russell SE. Expression of *SEPT9_i4* confers resistance to microtubule interacting drugs, *Cell Oncol* 2012 ; 35(2):85–93.
4. McDade SS, Hall PA, Russell SE. Translational control of *SEPT9* isoforms is perturbed in disease. *Hum Mol Genet*. 2007;16:742–52.

OTHER ACHIEVEMENTS

Peter Hall, MD, PhD, FRCPath, is also Editor in Chief of the Journal of Pathology, the highest ranked research Journal in pathology with a JIF of 7.23.

Translational Cancer Research

A major focus of the new department is the enhancement of translation of research into clinical settings. To that end this Section is being established and appointments are currently being made.

GENETICS

GENETICS

CHAIRMAN
Brian Meyer, PhD

ADMIN SUPPORT
Lilia Fernandez
Klea M. Edquiban
Ralyn Alma O. Castillo
Maritess Santiago
Emalyn Samonte

THE LAST 12 MONTHS HAVE SEEN MANY SIGNIFICANT ACHIEVEMENTS at the departmental and individual level. These have centred on the research, service, training and educational activities of the Department and are summarized in the following.

ACADEMIC ACHIEVEMENTS

1. Over 50 high quality publications related to hereditary disease and disease susceptibility.
2. Departmental scientists are engaged in more than 15 externally funded research grants totaling in excess of SAR 30 million.
3. Dr. Fowzan Alkuraya appointed as a Full Professor of Genetics by the School of Medicine, Al-Faisal University.
4. Dr. Dana Baheet appointed as Associate Dean for the Women's division, School of Medicine, Al-Faisal University.
5. Dr. Nada Al Tassan is serving as an unpaid consultant in both the Genome Chair and the Biochemistry Department at King Saud University.
6. Dr. Nada Al Tassan served as an examiner in 3 MSc. viva's at King Saud University.
7. Members serve on multiple editorial boards.
8. Members act as reviewers for more than 10 scientific journals.
9. Dr. Fowzan Alkuraya served as the external examiner for the Medical School, KSU.
10. Dr. Nada Al Tassan served as an examiner in 3 MSc. viva's at King Saud University.
11. Multiple International, National and intra-hospital collaborative research projects covering almost all areas of clinical medicine.

TRAINING AND EDUCATION ACHIEVEMENTS

1. Hosted almost 100 trainees ranging from gifted students, science and medical graduates to clinical fellows within the Department of Genetics.
2. Student Maha Al-Rasheed passed her MSc and transferred to a PhD program with Brighton University, UK.
3. Dr. Faiqa Imtiaz Ahmad completed a three-year Dubai Harvard Research Fellowship, hosted by the laboratory of Professor Cynthia Morton at Harvard Medical School, Boston in 2011.
4. Under the supervision of Dr. Nada Al Tassan, one student completed her Msc. project in the Behavioral Genetics Unit and was awarded her degree from KSU.

CLINICAL SERVICES

1. In 2011, under the supervision of Dr. Faiqa Imtiaz Ahmad, the Molecular Diagnostic Laboratory (MDL) successfully performed and reported on 130 prenatal diagnostic tests for over 50 different genetic diseases.
2. By the end of 2011, the FAHD Unit under the supervision of Dr. Faiqa Imtiaz Ahmad initiated, performed and reported on patients and their families with 95 different genetic diseases now available as a service at KFSH&RC. In particular, 50 of these genetic tests are designed to molecularly characterize inherited errors of metabolism, of which approximately 200 mutations (130 novel) have been reported by the FAHD Section.
3. Molecular Cytogenetic Assays were established for the Department of Pathology and Laboratory Medicine.
4. Screening of 120,000 plus newborns for Inborn errors of Metabolism including those from several non-ministerial and private hospitals.
5. Over 2,000 diagnostic samples processed for inherited diseases by the Molecular Diagnostic Laboratory.
6. Provision of molecular diagnostic tests through ICIS.

OTHER SERVICE WORK

1. The Equine Fingerprinting Unit has provided approximately 1200 parentage tests.
2. 2000 whole genome scans using the Affymetrix Axion platform provided to KSU on a fee for service basis. Resulted in the first Genome Wide Association Study performed on an Arab cohort.

CORE FACILITIES

1. The Sequencing Core Facility continues to work with maximum possible performance (400,000 sequencing reads and approximately 10,000 genotyping results.
2. Thirty whole Saudi exomes have been sequenced using Solid4 platform.

3. Over 10,000 microarrays processed for research and clinical purposes.

SCIENTIFIC AND TECHNICAL ACHIEVEMENTS

1. Establishment of whole genome and whole exome sequencing.
2. Establishment of a Next Generation Sequencing informatics pipeline.
3. Our first NGS finding (mutation in MGAT) was published (*Am. J. Hum. Genet.*) (in press)

During the next 12 months we anticipate significant expansion of our core facilities to advance our collaborative opportunities both nationally through agencies such as KACST and internationally both in Europe and North America. The activities of the Department of Genetics are progressing well and are well supported towards taking KFSH&RC to the cutting edge in this field.

Centrally supported research programs and services are the hallmarks of the Department of Genetics. In this regard work of the core and service facilities continue to increase substantially. They support and/or catalyze basic and translational research. It has been particularly satisfying to see this reflected in the number and impact of publications from the department during 2010 which included several that were institutionally recognized and awarded during the Research Centre's annual report. My congratulations are extended to the scientists, their collaborators and those who supported them in these achievements. Of particular note is the work of the Developmental Genetics, Gene Therapy and Behavioural Genetics sections of the department. As is consistently the case, both the National Laboratory for Newborn Screening and the Molecular Diagnostic Laboratory have extended the level of clinical service they provide. Of particular note is an increase in the number of hospitals served by the Newborn Screening Program and the rapid growth in number of cases processed by the Molecular Diagnostic Laboratory for prenatal diagnosis. During 2010 the department also continued to build its technological expertise and capacity having introduced Next generation sequencing, molecular karyotyping, high throughput genotyping and expanded bioinformatics capabilities to deal with these. The genotyping core facility supported the first Genome Wide Association Study conducted in the region. Similarly the sequencing core facility leads the region in exome sequencing which promises to be a major advance to our research capability in the coming year. We look forward to the contribution of these initiatives during the year ahead.

Behavioral Genetics

HEAD
Nada Al Tassan, PhD

MEMBERS
Dania Khalil, Bsc
Jameela Shinwari, Msc
Amna AlMagrashi, Bsc
Basma Al Tawil, Bsc
Aisha Omar, Bsc

The main objective of the unit is to explore the molecular basis of different disorders focusing mainly on multiplex families where trait segregates and also investigate sporadic single cases, which might give an insight in to the genetics of complex disorders and eventually may lead to an additional focus on improving clinical diagnosis, genetic testing and counseling for affected individuals and families in Saudi Arabia. In addition the unit provides diagnostic and research services to characterize mutations in different simple and complex diseases.

We are seeking to understand the mechanisms of development of different monogenic and complex disorders. The main interest in our laboratory is to identify novel causative and predisposing genes using a combination of homozygosity mapping, candidate gene screening and next generation sequencing. We successfully mapped two novel genes; PIK3R5 in a family with Ataxia Ocular Apraxia (Al Tassan et al 2012) and *ADAMTS17* in patients with Weill Marchesani like Syndrome (Morales et al 2009).

RESEARCH PROJECTS

PROJECT TITLE: **Molecular Analysis of APTX and SETX genes in Saudi Families with Ataxia Ocular Apraxia (AOA)**

RAC # 2050036

INVESTIGATORS: *AL-Tassan N, Bohlega S, Imtiaz F, Yamani S.*

PROJECT DESCRIPTION: The objective of the study is to identify families with the rare recessive disorders AOA types I and II, and screen for mutations in the common known genes *APTX*, *SETX* and *MRE11*.

PROJECT PROGRESS: Five families with AOA type I (family B, C, D)or II (family A and D) were enrolled in the study (2 or more affected individuals). Comprehensive screening for the whole open reading frame (ORF) of the related genes was performed and completed in all families. A novel truncating mutation (c.6859 C>T, R2287X) in exon 20 of the *SETX* gene was identified as the disease causing mutation in family A. The *MRE11* common reported mutation W210C was identified in two unrelated families with AOA1. Linkage and homozygosity mapping in family E with four affected individuals identified *PIK3R5* as novel causative gene with a missense mutation that segregates within the family.

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, FBN-1*).

PROJECT PROGRESS: Sequencing of the whole coding region of the related genes (*ADAMTS-10, FBN1*) is being performed in affected individuals from families with WMS phenotype. Three novel missense mutations in *ADAMTS10* were identified in three families. In addition to the three mutations identified in *ADAMTS17* the gene mapped by this group in 2009, two additional novel mutations were identified in new recruited cases. Homozygosity mapping identified a novel locus in a family, candidate gene screening is ongoing.

PROJECT TITLE: **Genetic evaluation of congenital eyelid and eye movement abnormalities**

RAC # 2080020

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

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

PROJECT PROGRESS: Comprehensive screening for the whole open reading frame (ORF) of *KIF21A* was performed and completed in affected individuals. The common R954W missense mutation was identified in two families with dominant form of the disorder. A mosaic mutation R954L in *KIF12A* was identified in two siblings with CFEOM2. Sixty other patients have been enrolled in the study and mutational screenings have revealed several novel and reported polymorphisms in some of these genes and novel *ROBO3* missense mutation P771L was identified in a patient with synergistic convergence. A splice mutation in *FRMD7* in siblings with x-linked nestagmous was also identified.

Twenty two families (2 or more affected) are being analyzed to identify potential novel disease loci; several novel loci have been identified. These regions are being further investigated using whole exome next generation sequencing and bidirectional sequencing of candidate genes. Several variants have been identified and are being investigated further.

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

RAC # 2080020

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

PROJECT DESCRIPTION: This multidisciplinary multicentre study aims to investigate the genetic basis of ASD patients in Saudi Arabia using genome-wide linkage analysis of ASD families with 3 or more affected individuals using microarray based genotyping. Simplex cases (100) will also be studied using a homozygosity based approach to identify underlying genes.

PROJECT PROGRESS: Seventy Five families (multiplex and single) enrolled so far, Linkage analysis have revealed candidate loci on chromosome 7 in one family, Next generation sequencing of one affected individual in this family identified a number of potential disease causing variants.

Homozygosity mapping and sib-pair analysis in families with 2 affected individuals identified 3 shared disease loci on chromosomes 3p11, 4q11-q12, 14q23.3-q24.1. Genes in these regions are being further investigated. In addition, a missense variant was identified in a family with two affected individuals, which being investigated further.

PROJECT TITLE: **Genetic characterization of Hemoglobinopathies in Saudi Arabia**

RAC # 2080012

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

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

PROJECT PROGRESS: 110 β- thalassaemia patients were enrolled from KKUH and KFSHRC. Screening of the β- globin gene identified a 9 mutations and 53 variants some of these are novel. Haplotyping of these patients was generated using 7 RE.

PROJECT TITLE: **Identification of Sulfonylurea Receptor SUR1 and Potassium Inward Rectifying Receptor Kir6.2 Genes mutations in Saudi patients with persistent hyperinsulenimic 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 PHHI and enroll them to screen for mutations in *SUR1/Kir6.2* receptors gene in the entire genomic sequence.

PROJECT 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.

PROJECT TITLE: **The Molecular Basis of Inherited Reproductive Disorders**

RAC # 2091054)

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

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

PROJECT PROGRESS: The sequencing of all patients for 16 genes was completed; a number of novel and previously reported mutations were identified and reported. Whole Exome Sequencing of a family with 5 affected individuals identified a number of patiently pathogenic variants that are currently being validated.

KACST FUNDED PROJECTS

PROJECT TITLE: **The Molecular Basis of Parkinson's Disease in Saudis**

RAC # 2110035 (NCPST SR2,000,000)

INVESTIGATORS: *Al Tassan N, AlKairallah T, Bohlega S, Imtaiz F.*

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

PROJECT PROGRESS: Screening for the reported genes is ongoing.

FUTURE RESEARCH DIRECTION

The main future goal is to establish a research facility that utilizes the latest molecular analysis techniques to study genetically diverse complex disorders not limited to identify new disease causing genes and novel mutations but also to study the functional role of these mutations and the mechanism underlying the development of these genetic disorders.

PUBLICATIONS AND POSTERS (YEAR 2011)

- Khalak HG, Wakil SM, Imtiaz F, Ramzan K, Baz B, Almostafa A, Hagos S, Alzahrani F, Abu-Dhaim N, Abu Safieh L et al: Autozygome maps dispensable DNA and reveals potential selective bias against nullizygosity. *Genet Med* 2012.
- Al Tassan N, Khalil D, Shinwari J, Al Sharif L, Bavi P, Abduljaleel Z, Abu Dhaim N, Magrashi A, Bobis S, Ahmed H et al: A missense mutation in PIK3R5 gene in a family with ataxia and oculomotor apraxia. *Hum Mutat* 2012, 33(2):351-354.
- Khan AO, Shinwari J, Al-Sharif L, Khalil DS, Al Tassan N: Prolonged pursuit by optokinetic drum testing in asymptomatic female carriers of novel FRMD7 splice mutation c.1050 +5 G>A. *Arch Ophthalmol* 2011, 129(7):936-940.
- Khan AO, Shinwari J, Al Sharif L, Khalil D, Al-Gehedan S, Tassan NA: Infantile esotropia could be oligogenic and allelic with Duane retraction syndrome. *Mol Vis* 2011, 17:1997-2002.
- Bazzi MD, Sultan MA, Al Tassan N, Alanazi M, Al-Amri A, Al-Hajjaj MS, Al-Muhsen S, Alba-Concepcion K, Warsy A: Interleukin 17A and F and asthma in Saudi Arabia: gene polymorphisms and protein levels. *J Investig Allergol Clin Immunol* 2011, 21(7):551-555.
- Shinwari J, Alamri A, Alanazi M, AL Tassan N. Screening for variants in the MUTYH gene in *Saudis Open Journal of Genetics* 2011, 3:70-77.
- Shinwari J, Adi A, Aldosari M, Khalil. D, Abu-Doheim N, Almuslamani A, Nester M, Ghannam M, Meyer BF and Al Tassan N. Loss of Heterozygosity Analysis in Saudi Patients with ASD. *IMFAR* 2011, USA May 2011 (Poster).

Cardiovascular and Pharmacogenomics

HEAD
Nduna Dzimiri, PhD

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

The cardiovascular and pharmacogenomics unit currently focuses 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. To achieve this objective, we employ a three-pronged approach of (1) linkage analysis using Affymetrix whole genome scan 250 sty1 array platform (2) genome-wide association study on Affymetrix axiom platform and (3) targeted population-based studies on individual genes using the Taqman assay on ABI real-time PCR system.

Thus far, linkage analysis has been performed to study early onset of coronary artery disease in heterozygous familial hyperlipidaemia setting, which indentified a number of chromosomal loci as potential risk for this phenomenon. This has led to searching for potential target genes and gene variants at these loci, and identification of novel mutations in suspect genes.

We have also recently run genome-wide scanning of about 5000 individuals with CAD and/or one of its important risk traits, such as hypertension, type 2 diabetes mellitus, obesity and dyslipidaemia. Analysis of these results is in progress. With respect to population-based association studies, during the current report period, we were able to assess the role(s) of several variants of interest in various risk genes (<10 for each gene), including in particular, angiotensinogen, thrombospondin (TSB), apolipoprotein B, paraoxonases 1 and lympotoxin among others, to expand our previous findings in smaller population sizes on a some of these genes. We were able to describe some pleiotropic effects of genes such as AGT and TSB on various CAD risk traits, including dyslipidaemia and metabolic syndrome, as possibly explaining some of the genetic basis for disease pathways leading to atherosclerosis. Besides, our findings also confirmed our notion that events associated with the function of the 3 prime untranslated (3'UTR) region are an integral part of such disease process mechanisms, especially for complex disease such as CAD. The synopsis of these results is discussed below under the respective projects.

Importantly, the Unit is currently in the process of establishing a Pharmacogenomics Test Laboratory in line with the setting up of a regional PGENI program at KFSH&RC. Furthermore, in this period we also worked on five projects with collaborators both at national and international levels.

RESEARCH PROJECTS

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

RAC # 2010 020

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

PROJECT DESCRIPTION: This study evaluates the role of gene polymorphism(s) in CAD and its risk traits, using the Saudi population as a study model. This is accomplished by both whole genome scanning approach using the Affymerix Axion platform and by first identifying single nucleotide polymorphisms (SNPs) in genes of interest in the general population followed by association studies using Taqman assays on the ABI real-time PCR system in a population of >5,000 individuals. These individuals may be CAD patients, or may harbor one or more of the risk diseases, such as hypertension, type 2 diabetes, dyslipidaemia in the Saudi population.

PROGRESS: During the report period, our efforts were focussed on running the whole-genome scanning for the individuals in the CAD database as well as performing the real-time PCR for previously identified variants in our genes of interest. In summary, thus far the running of Affymetrix assays has been accomplished for about 5,000 individuals and data analysis is in progress. Furthermore, association studies have been performed for specific genes in these individuals. In summary, 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 genes constitute important risk for diseases such as CAD, an issue we are now 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 # 2030 012

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

PROJECT DESCRIPTION: This study aims at identifying mutations in candidate genes for dyslipidemic disorders, as well as intra-individual differences in patient responses to drug therapy of antihyperlipidaemia treatment with statins (lipid lowering agents). We employ a two-pronged approach involving (a) linkage studies for early onset of CAD using Affymetrix whole genome scan 250 sty1 array and (b) population-based association analysis employing our CAD database by Taqman assays on the ABI system.

PROGRESS: Linkage studies thus far in two Saudi families with heterozygous familial hypercholesterolemia (HFH) have yielded a wealth of information regarding possible loci linking early onset CAD with familial hypercholesterolaemia. We have selected a number of potential genes at these chromosomal loci for association studies. Thus far, our ongoing studies point to pleitropic effects of a number of genes, including thrombospondin and adiponectin in risk traits for metabolic disorders, type 2 diabetes and hypertension, which might explain some common pathways for CAD risk factors leading to the manifestation of atherosclerosis.

PROJECT TITLE: **Clinical and molecular characterization of patients with inherited arrhythmogenic disorders**

RAC # 2050 035

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

PROJECT DESCRIPTION: This study aims at identifying genes responsible for 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 confirmation of patient diagnosis stratification and prophylactical strategies in the management of patients with arrhythmogenic disorders.

PROGRESS: More than forty Saudi families with various forms of inherited arrhythmogenic disorders (IAD) have been recruited, several of which had Romano-Ward syndrome (RWS), Jervell and Lange-Nielsen, Brugada syndrome, sick sinus syndrome, arrhythmogenic right venricular dysplasia and catecholaminegic polymorphic ventricular tachycardia. Several genes known to be associated with IAD were tested in these families. In summary, more than 5 families harboured heterozygous mutation in KCNQ1 and 1 in PKP2, 4 families showed homozygous mutations in KCNQ1, I in CASQ1 and 1 SCN5A genes. These data thus far represents the largest cohort of Arab patients and illustrates the impact of high degree of consanguinity on causative genotypes for IAD.

PROJECT TITLE: **The role of gene polymorphism in the regulation of the thyroid stimulating hormone level**

RAC # 2100 025

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

PROJECT DESCRIPTION: The 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; i.e. hyperthyroidism suppresses TSH secretion while hypothyroidism stimulates it. The normal serum TSH range (0.5–5.0 U/l) is relatively wide, and it is not quite clear what determines its level in an individual. Furthermore, recent studies have shown an association between the risk of differentiated thyroid cancer (DTC) and the high TSH level within normal range. We hypothesize that TSH levels are related to presence of variations in some gene(s) involved 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: Thus far, screening for mutations in the 6 genes, (DIO1, DIO2, DIO3 NIS, TSHB and PAX8) has been accomplished, in order to identify prevalent variants of potential interest in the Saudi population. This has led to the discovery of several novel insertion/deletion as well as non-synonymous polymorphic changes in NIS, DIO2, TSHB and PAX8. Association studies are in progress for selected gene variants.

PROJECT TITLE: **Role of the scaffold protein striatin in regulating cardiac remodelling**

RAC # 2100 026

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 mutlifunctional 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 has been 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 arrythmogenic right ventricle tachycardia with a deletion of the 3' untranslated region of striatin gene resulting in reduced mRNA production, while biochemical analysis revealed that the interaction between striatin and calmodulin or caveolin is calcium sensitive. This is suggestive of an important role for striatin in regulating cardiomyocytes dynamics.

Having successfully identifying striatin in the heart, we are proposing to evaluate its role in the evolution of cardiac remodeling by studying its expression level during normal cardiac development with emphasis on molecular aspects in regulating myocardial remodelling. We will be manipulating the levels of striatin by employing knock down and overexpression procedures and 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 first verified the expression of striatin in our proposed model and found that it is highly expressed in rat myocardium. Ensuing experiments, including immunoprecipitation and calmodulin pull down assay, showed 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. Furthermore, striatin associates with cardiac ryanodine receptor type 2 RyR2, a finding that we are now pursuing. There was no evidence of interaction between striatin and PP2A in the heart. In a preliminary attempt we have also found that, in the heart, striatin is associated with a network of proteins (~35 potential targets) that is also worth of decoding.

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Books, book chapters and review articles

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Abstracts and scientific conference proceedings

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- Wakil S, Al-Najai M, Andres E, Elhawari S, Vigilla MG, Gueco D, Muiya P, Alshahid M and Dzimiri N. The adiponectin Q is a susceptibility gene for metabolic syndrome. 12th ASHG Congress, Montreal, October, 11–15, 2011.
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- Muiya PN, Elhawari S, Andres E, Meyer BF, Al-Mohanna F, Alshahid M, and Dzimiri N. The AGT is a susceptibility gene for coronary artery disease. Experimental Biology 2011, Washington DC, April 9–13, 2011.
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Cognitive Genetics

HEAD
Namik Kaya, MSc, PhD

MEMBERS
Mazhor Al-Dosary, MSc, PhD
(Recently Joined)
AlBandary AlBakheet, MSc

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

MISSION AND GOALS

Altogether neurogenetic, neurodevelopmental, psychiatric and behavioral diseases are very common (10:100) in the Kingdom. Our mission is to explore hereditary causes 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

PROJECT TITLE: **Positional Cloning of genes underlying genetics disorders with prominent neuro-developmental manifestations in several extended families**

RAC# 2060 035

INVESTIGATORS: *N Kaya (PI), M Al-Sayeed (Co-PI), D Colak (Co-I)*

PROJECT DESCRIPTION: The specific aim of this project is to determine gene(s) ore regions that are critical and likely to play a role on the manifestations of genetic disorders with prominent neurodevelopmental features. We will utilize high density Affymetrix arrays such as Affymetrix 6.0, 500K, and axiom custom gentyping arrays to perform genotyping, copy number analysis, linkage, and homozygosity mapping on the patients' samples. Microsatellite markers are also utilized for fine mapping in order narrow down the linkage intervals and shared LOH blocks.

PROGRESS: DNA samples have been collected from consanguineous families. SNP-based genotyping, linkage analysis, homozygosity mapping and mutation analysis were performed. Copy number analyses were also integrated to the analysis to determine likely gross deletions. Two manuscript is already published in peer-review journals and two others are currently under review.

PROJECT TITLE: **Genetic Basis of Mental Retardation in Families from KSA**

RAC# 2080-036

INVESTIGATORS: *Meyer B (PI), Kaya N (Co-I), Sakati N (Co-I), Al-Owain M (Co-I), Alsayed M (Co-I), Hassnan Z (Co-I), Alkuraya F (Co-I), Dalaan H (Co-I), Yemani S (Co-I), Semmari A (Co-I),*

PROJECT DESCRIPTION: The specific aims of the project is 1) to identify and ascertain pedigrees with autosomal recessive (AR) mental retardation (MR) in the UAE and KSA populations and perform full clinical characterization of the affected individuals, 2) to map underlying AR-MR loci, some of which are likely to be novel, 3) to identify regional alleles of known genes and causative genes for AR-MR and undertake functional studies of novel causative genes.

PROGRESS: Biological samples based on inclusion criteria have been collected from numerous families. We have performed linkage analysis and homozygosity mapping on all of these families using Affymetrix 250K and axiom mapping/genotyping arrays and narrowed down the linked regions using microsatellites. Targeted sequencing is ongoing for the selected genes.

INTERNATIONAL COLLABORATOR: Christopher Walsh, Genetics Department, Harvard International and Harvard University, Boston, UK

PROJECT TITLE: Molecular genetic studies in chromosome disorders. RAC #2040 042.

INVESTIGATORS: *Kaya N (PI), Colak D, Sakati N, Al-Owain M, Al-Odaib A, Alkuraya F, Al-Dosari N, Walter C, Hassnan Z, Iqbal M.*

PROJECT DESCRIPTION: The specific aim of this project is to identify a chromosomal aberration/abnormality in patients who are suspected to have such abnormalities whether he/she may have dysmorphia or other clinically relevant symptoms. Once suspected and found, such abnormalities will be assessed whether they are inherited and shared among related individuals or sporadically appeared as *de novo*. In familial cases we also utilize linkage and homozygosity mapping to identify small scale abnormalities such as deletions, and duplications in such patients. Another objective of the project is to study complex rearrangements including balanced and unbalanced translocations, and inversions.

PROGRESS: We have been collecting samples from patients based on our inclusion criteria. We have performed high-resolution karyotyping using Agilent's high-density genome-wide karyotyping chips (44K and 244K). Similarly we also utilized Affymetrix's Genome-Wide Human SNP Array 6.0 assays for SNP and CNV based molecular karyotyping. Moreover, linkage and homozygosity mapping and genome-wide gene expression studies using Affymetrix GeneChip SNP and gene expression assays were also performed on selected families/patients. Recently we started to utilize Affymetrix® Cytogenetics Whole-Genome 2.7M Array, highest density array available for molecular cytogenetics applications. We have published two articles using the 244K (Agilent) datasets. Additional three manuscripts has been under review by peer review journals and recently accepted for publication. In addition to Agilent data sets we are currently investigating the allelic frequencies of these CNVs in the normal individuals in the Saudi population. This is very essential for our cytogenetics studies in order to discriminate a benign CNV from a malignant CNV. We have been also targeting and sequencing the candidate genes based on our linkage and homozygosity mapping studies to identify disease causing mutations and gene/s in our patients.

PROJECT TITLE: **Pathogenesis of Early Infantile Primary Lactic Acidosis**

RAC # 2050-009

INVESTIGATORS: *Al-Owain M (PI), Kaya N (Co-PI), Ali Al-Odaib, Colak D, Al-Hassnan Z*

PROJECT DESCRIPTION: This study aims to establish the sequence of pathological events in early infantile lactic acidosis patients. This will be achieved by serially studying the apoptosis and the derangement of the nuclear/mitochondrial oxidative phosphorylation (OXPHOS) genes and their transcription profiling in such infants. ABI 1700 Microarray Analyzer will be utilized for expression profiling in whole blood samples from our patients. Linkage experiments as well as fine mapping studies will be also performed on familial cases.

PROGRESS: We have recruited several patients from different parts of Saudi Arabia. Global gene expression profiling was performed on samples from patients and age and sex matching controls using ABI 1700 system. Data analyses were performed by using several statistical and bioinformatics tools. The differentially expressed genes in patients compared to controls have been determined with statistical significance. The unsupervised analysis clearly separated individuals based on their subject group. Functional annotation and biological term enrichment analysis were performed. Pathway and functional network analyses were finalized. A manuscript was prepared and submitted to a high impact peer-review genomics journal. Also, Linkage and homozygosity mapping studies were performed on familial cases. Fine mapping and sequencing of targeted genes were completed on an extended large family. The results of this study were submitted to a high-impact peer-review neurology journal.

INTERNATIONAL COLLABORATOR: Robert W. Taylor, Mitochondrial Group, Newcastle University, Newcastle upon Tyne, UK

PROJECT TITLE: **Molecular Studies on Mitochondrial Diseases in Saudi Arabia (KACST/Under Review)**

INVESTIGATORS: *Kaya N (PI), Al-Owain M (Co-PI), Al- Muhaizea M, Al-Hindi H, Al-Zaidan H, Al-Dosary M, Alfadhel M*

PROJECT DESCRIPTION: Our main aim is to ascertain patients with suspected mitochondrial disorders with subsequent identification of the disease causing mtDNA or nuclear gene/mutations using state of art molecular approach and technologies. We expect to characterize novel nuclear genes causing mitochondriopathies that will shed light for other researchers on molecular mechanisms of such diseases and could ultimately lay the ground for potential therapies in the future. In addition, our results will have significant impact on drawing the mutational landscape of mitochondrial disorders in KSA. Furthermore, the knowledge gained from our study will be utilized by molecular laboratories in KSA for diagnosis of these conditions. Finally, the results will be the basis for a preventative program for mitochondrial genetic diseases.

PROGRESS: Project is under review by KACST/AAAS

INTERNATIONAL COLLABORATOR: Robert W. Taylor, Mitochondrial Group, Newcastle University, Newcastle upon Tyne, UK

Overall, we have published 25 peer-reviewed journal articles in prestigious journals and two book chapters in respected publishers from May 2008 to Jan 2012.

RECENT PUBLICATIONS

Research Articles Published in Peer Reviewed Journals

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Developmental Genetics

HEAD

Fowzan Al Kuraya, MD, FAAP, FACMG

MEMBERS

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Farah Hindieh
Dr. Racad Hammami

The developmental genetics section is focused on studying the genetic control of normal human development. Although our focus has been on mapping Mendelian birth defects that involve the eye and craniofacial region, we have recently expanded our interest to include Mendelian phenocopies of common diseases capitalizing on our success with autozygome analysis. Our unit employs cutting edge techniques in the area of developmental genetics with close ties to the Comparative Medicine Department and we are excited about the impending establishment of the zebrafish transgenic facility, which will greatly improve the quality of research in our unit.

RESEARCH ACTIVITIES

There are on-going approved funded projects;

- Genetics of Craniofacial Birth Defects in Saudi Arabia
- Genetics of Vision Loss in Saudi Arabia
- Genetics of Osteogenesis Imperfecta in Saudi Arabia
- In Search of Genetics Determinants of Diabetic Retinopathy
- Carrier Phenome Project

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First Arabian Hereditary Deafness (FAHD)

HEAD
Faiqa Imtiaz Ahmad, PhD

MEMBERS
Khushnooda Ramzan, PhD
Danyah Trabzuni *(PhD Student)*
Bashayer Al-Mubarak *(PhD Student)*
Rabab Allam
Abeer Al Mostafa
Lolwa Gomaa
Amal Berhan

The main research aspect of the FAHD section is to try and identify known and novel genes causing hereditary non-syndromic and syndromic hearing loss in the Saudi Arabian population (KACST#08-MED49520-: RAC# 2100 001). We are also co-investigators in two approved projects investigating the molecular basis of Laron Syndrome (RAC# 2101 034) and Parkinson's Disease (RAC # 2110 035) in Saudi Arabian patients. In addition, 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 and around the kingdom. To date, we have initiated, performed and reported on patients and their families with over 100 different genetic diseases now available at KFSH&RC. In particular, 50 of these genetic tests are designed to molecularly characterize inherited errors of metabolism, of which approximately 200 mutations (100 novel) have been reported. Furthermore, in 2011 under the supervision of Dr. Faiqa Imtiaz Ahmad, the Saudi Diagnostic Laboratory (SDL) successfully performed and reported on 130 prenatal diagnostic tests for over 50 different genetic diseases. Our ultimate goal is to help lay the foundation for preventative measures including carrier testing, counseling, prenatal diagnosis, pre-implantation genetic diagnosis and pre-marital screening.

RESEARCH PROJECTS

PROJECT TITLE: **Molecular Characterization of Hereditary Deafness in Saudi Population**

RAC# 2100 001/KACST#08-MED495-20

INVESTIGATORS: *Dr Faiqa Imtiaz (PhD), Dr Mohammad Al-Owain (MD), Dr Khushnooda Ramzan (PhD), Dr Selwa Al-Hazzaa (MD), Ms Ghada Bin-Khamis (MA)*

PROJECT DESCRIPTION: Recessively inherited diseases are more prevalent in populations 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%) and environmental (50%) etiologies. Our study hopes to define the genetics of 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.

PROGRESS:

- 2-year project to study hereditary deafness awarded and funded by KACST in 2009.
- 3 year fellowship awarded to Dr. Faiqa Imtiaz from the Dubai Harvard Foundation, between KFSH&RC and the laboratory of Professor Cynthia Morton at Harvard Medical School for the investigation of the genetic causes of hereditary deafness in Saudi Arabia.
- Successfully completed 3-year PSCDR funded project to study "Role of DFNB1 in the Saudi Population".

PROJECT TITLE: **Clinical and Molecular Basis of Laron Syndrome Patients in Saudi Arabia**

RAC# 2101 034

INVESTIGATORS: *Dr Faiqa Imtiaz (PhD), Dr Mohammad Al-Owain (MD), Dr. Abdullah Al-Ashwal (MD), Alya Qari (MSc)*

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

PROGRESS: We have currently found the disease-causing mutation in 40 of the 45 patients enrolled in this study.

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Gene Therapy

HEAD
Yufei Shi, PhD

MEMBERS
Minjing Zou
Essa Baitei
Roua Al-Rijjal
Faisal Bin Humaid

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 could prevent or reduce tumor development and progression. We also conducted a genetic study of a Saudi family with multiple endocrine neoplasia type 1 and found a novel 5 kb deletion in the *MEN1* promoter and exon 1 and 2. LOH analysis of tumor tissue indicated somatic deletion of maternal chromosome 11 including *MEN1* locus (11q13) and 11p15 imprinting region. Chromosome 11p15 contains a cluster of imprinted genes involved in fetal growth and cancer. Immunohistochemistry analysis showed that the expression of paternally expressed *IGF-II* was up-regulated and the maternally expressed *CDKN1C/p57KIP2* was lost in the pancreatic islet cell tumors. These data suggest that somatic imprinting disruption of 11p15 may be involved in the tumor development.

RESEARCH PROJECTS

PROJECT TITLE: **IL-12 Gene Therapy of Thyroid Cancer in BRAF^{V600E} Transgenic Mouse Model**

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

PROJECT DESCRIPTION: Thyroid carcinoma is the second most common malignancy among Saudi female cancer patients. There are three types of thyroid carcinoma derived from thyroid follicular cells: papillary, follicular, and anaplastic carcinomas. Papillary thyroid carcinomas (PTC) are the most common type, accounting for more than 80% thyroid malignancies. *BRAF*^{V600E} mutations are frequently identified in more than 40% PTC. Although most differentiated thyroid carcinomas can be cured by surgery and ^{131}I therapy, 10–20% patients are refractory to the conventional therapy and die from recurrence or progression into poorly differentiated tumors. No effective treatment is currently available for these patients, making it necessary to develop novel therapeutic approaches. Interleukin 12 (IL-12) is a proinflammatory heterodimeric cytokine with strong antitumor activity. Our previous studies have shown that IL-12 gene therapy is effective against anaplastic thyroid carcinoma in a nude mice xenograft tumor model. In the current project, we plan to investigate IL-12 gene therapy against *BRAF*^{V600E} mutation induced thyroid tumors in *BRAF*^{V600E} transgenic mice. Since *BRAF*^{V600E} transgenic mice are more resemble to natural thyroid tumorigenesis and T cells in these mice are functional, this would allow us to further evaluate the effectiveness of IL-12 gene therapy against thyroid cancer and T cell mediated anti-tumor activity induced by IL-12. Given that *BRAF*^{V600E} is present in more than 40% PTC, the effectiveness of IL-12 against thyroid tumorigenesis in *BRAF*^{V600E} transgenic mice would provide further support for its clinical use. If IL-12 is shown to be effective in preventing tumor development, a new therapeutic/preventive strategy may be developed for thyroid cancer patients to eliminate residual tumor cells after surgery or treat/prevent development of metastatic disease.

PROJECT PROGRESS: Preliminary studies have shown that IL-12 could prevent or reduce tumor development and progression in *BRAF*^{V600E} transgenic mice. The project has been submitted to KACST for funding.

PROJECT TITLE: **Molecular Characterization of the Mechanisms in BRAF Splicing Variants and Pseudogene Mediated Signalling and Thyroid Tumorigenesis in Transgenic Mice**

Biotechnology grant#10-BI0957-20

INVESTIGATORS: *Yufei Shi, Ali Al-Zaharani, Minjing Zou, Essa Y Baitei*

PROJECT DESCRIPTION: Activating *BRAF*^{V600E} mutations have been reported in about 40% of papillary thyroid carcinomas (PTC). Recently, we have identified novel BRAF splicing variants in PTC. These splicing variants can activate MAP kinase signalling pathway and induce tumors in nude mice, therefore, functioning as an alternative mechanism for oncogenic *BRAF* activation. We have also found that BRAF pseudogene is expressed in some benign thyroid goiters and early stages of PTC tumors and there is an inverse association between *BRAF* pseudogene expression and BRAF mutation. Overexpression of BRAF pseudogene can activate MAP kinase signalling pathway and induce tumors in nude mice as well. However, given the fact that *BRAF* variants and its pseudogene have no kinase activity, we hypothesize that they may interact with ARAF, BRAF, or CRAF to activate MAP kinase. In the present study, we would like to investigate the mechanisms on how the splicing variants and pseudogene activate MAP kinase signalling pathway.

PROGRESS: The project is funded by KACST and is progressing as planned. We found that CRAF is not involved in *BRAF* variants-induced MAPK activation. ARAF may be involved.

PROJECT TITLE: **Genetic Study and phenotype-genotype correlation of a Saudi Family with Multiple Endocrine Neoplasia type 1**

RAC # 2091027

INVESTIGATORS: *Hussein Raef, and Yufei Shi*

PROJECT DESCRIPTION: The common features of multiple endocrine neoplasia (*MEN1*) include primary hyperparathyroidism secondary to parathyroid hyperplasia in most patients, pituitary adenomas in up to 30–40% of patients, and pancreatic tumors in 35–70% of cases. Other features include carcinoid tumors and silent adrenal adenomas. We encountered a large Saudi family with *MEN1* in whom, malignant pancreatic tumors were present in the father and 3 of his children who had clinical disease, and were the presenting features in 2 subjects. In one subject with gastrinoma, insulin was also co-secreted and resulted in severe hypoglycemia. Adrenal adenomas were also seen in all 4 subjects with clinically proven disease, and in one patient the adenoma resulted in florid Cushing's syndrome and DKA. The underlying molecular defects were investigated.

PROGRESS: We have characterized a large Saudi family with MEN1 with aggressive tumor behavior: malignant pancreatic islet cell tumors were present in 5 affected subjects and were the presenting features in 3 subjects. Mutation screening by PCR-sequence analysis of patients' peripheral blood DNA did not reveal any mutation in the *MEN1* or *CDKN1B* gene. Gene copy number analysis by multiplex ligation-dependent probe amplification (MLPA) and array comparative genomic hybridization (aCGH) demonstrated a novel monoallelic deletion of 5 kb genomic DNA involving *MEN1* promoter, exon 1 and 2. LOH analysis of tumor tissue indicated somatic deletion of maternal chromosome 11 including MEN1 locus (11q13) and 11p15 imprinting region. Chromosome 11p15 contains a cluster of imprinted genes involved in fetal growth and cancer. Immunohistochemistry analysis showed that the expression of paternally expressed *IGF-II* was up-regulated and the maternally expressed *CDKN1C/ p57KIP2* was lost in the pancreatic islet cell tumors. These data suggest that somatic imprinting disruption of 11p15 may be involved in the tumor development. The level of IGF-II up-regulation and/or *CDKN1C/ p57KIP2* down-regulation may contribute to an aggressive phenotype. The current study shed new light on the mechanisms of MEN1 pathogenesis.

PROJECT TITLE: **Investigation of the Genetic Defects of Severe Insulin Resistance Syndromes and in Patients with Diabetes Mellitus Type 2**

RAC# 2090024

INVESTIGATORS: *Ali Al-Zahrani and Yufei Shi*

PROJECT DESCRIPTION: Insulin resistance is an integral part of the pathogenesis of type 2 diabetes. Its underlying mechanisms are largely unknown. On the other hand, severe insulin resistance syndromes are rare and frequently associated with gene mutations in the insulin signaling pathway. In this study, we have identified 5 unrelated families with extreme insulin resistance syndrome type A in whom we have identified a novel biallelic mutation in the insulin binding domain of the insulin receptor.

PROGRESS: To investigate the underlying genetic defect, the entire coding region and intron-exon boundaries of the insulin receptor gene were PCR-amplified and sequenced from peripheral leukocyte DNA isolated from the patients and their healthy relatives. A biallelic R118C mutation in the binding domain of the insulin receptor was found in all the patients. A monoallelic R118C or wild type was present in healthy subjects in a pattern consistent with autosomal recessive inheritance. The R118C was not present in 100 normal population controls and the arginine residue is highly conserved among different species. The wild type and mutant R118C insulin receptor cDNA were cloned and expressed in CHO cells for functional analysis. As expected, no insulin binding was observed in mutant R118C transfected CHO cells. Western blot analysis showed that both wild type and mutant R118C are expressed equally in CHO cells. Confocal microscopy demonstrated that the mutant R118C are expressed on the cell surface and not retained in the endoplasmic reticulum. We conclude that the severe insulin resistance syndrome in these families is caused by biallelic germline R118C mutation in the insulin receptor gene, which renders the receptor unable to bind insulin to transmit the signal. Given that the same mutation is present in 5 unrelated families, it is likely that this is a founder mutation present in Arab population.

PUBLICATIONS

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- A Novel Deletion of MEN1 Gene in a Large Family of Multiple Endocrine Neoplasia Type 1 (MEN1) with Aggressive Phenotype. Raef H, Zou MJ, Baitei EY, Al-Rijjal RA, Kaya N, Al-Hamed M, Monies D, Abu-Dheim NN, Al-Hindi H, Al-Ghamdi MH, Meyer BF, and Shi Y. *Clin Endocrinol* (Oxf). 75(6):791-800, 2011
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Genotyping Core Facility

HEAD
Salma Wakil, PhD

MEMBERS
Batool Baz, Msc
Samiya Hagos, Bsc (*Grant*)
Haya Al Dusery, Bsc *(Grant)*

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.

Besides the 7 G GeneChip Stations, the laboratory is equipped with high throughput workflow which enables us to process approx. 760 samples in two weeks time with Axiom Genome Wide Human Array Plate. The Axiom genotyping solution is the newest line of product which enables to perform population optimized genome wide association studies, replication studies and candidate gene studies. This fully automated workflow utilizes GeneTitan Multi Channel (MC) instrument and automated target preparation on the Beckman Biomek FX Target Prep Express system.

Besides providing data which amount to 60 percent of work for mapping mendelian disorders. Last year we finished genotyping 1600 samples for Hepatitis B & C Virus association studies. At the moment we are genotyping samples for doing large association studies for Coronary Artery Disorders.

We are running the cytogenetic microarray which is again a high resolution array to detect broad range of chromosomal aberrations, detects uni-parental disomy and regions that are identical by descent. We have added another Microarray to our laboratory this year which is called DMET microarray which is the most comprehensive that enable to use pharmacogenetic markers for drug metabolism studies.

Apart from processing and running the microarrays, research projects are also undertaken at the unit.

RESEARCH PROJECTS

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

PROJECT DESCRIPTION AND STATUS: In this number of families have been collected and linkage analysis has been done. In at least, 4 families we have identified the mutation causing the disease in these families. Further more families are being analysed and paper was accepted and other paper is in preparation.

PROJECT TITLE: **Mapping of X-linked diseases with mitochondrial abnormalities.**

PROJECT STATUS: Paper accepted in Clinical Dysmorphology.

PROJECT TITLE: **Clinical and molecular characterization of patients with inherited arrhymogenic disorders.**

PROJECT DESCRIPTION: This project is in collaboration with pharmacogenetics unit where the candidates involved for LQT and other arrhythmogenic disorders are screened.

PROJECT STATUS: Paper accepted in American Journal of Cardiology

PROJECT TITLE: **Localization of Familial Juvenile Rhematoid Arthritis.**

PROJECT DESCRIPTION: The objective of this study is 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. Functional studies are ongoing to study the disease mechanism for this novel gene with unknown function. We have seen the expression profile of this gene in some cell lines and further experiments for localization of this gene.

PUBLICATIONS

- Recessively Inherited Severe Aortic Aneurysm Caused by Mutated EFEMP2. Al-Hassnan ZN, Almesned AR, Tulbah S, Hakami A, Al-Omrani A, Al Sehly A, Mohammed S, Majid S, Meyer B, Al-Fayyadh M. *Am J Cardiol*. 2012 Mar 20. [Epub ahead of print]
- Autosomal recessive hereditary spastic paraplegia with thin corpus callosum among Saudis. Wakil SM, Murad HN, Baz BM, Hagos ST, Al-Amr RA, Al-Yamani SA, Al-Wadaee SM, Meyer BF, Bohlega SA. *Neurosciences* (Riyadh). 2012 Jan;17(1):48-52.
- Autozygome maps dispensable DNA and reveals potential selective bias against nullizygosity. Khalak HG, Wakil SM, Imtiaz F, Ramzan K, Baz B, Almostafa A, Hagos S, Alzahrani F, Abu-Dhaim N, Abu Safieh L, Al-Jbali L, Al-Hamed MS, Monies D, Aldahmesh M, Al-Dosari MS, Kaya N, Shamseldin H, Shaheen R, Al-Rashed M, Hashem M, Al-Tassan N, Meyer B, Alazami AM, Alkuraya FS. *Genet Med*. 2012 Jan 5. doi: 10.1038/gim.2011.28. [Epub ahead of print]
- Subcutaneous nodules, arthropathy, coarse face, cataract and glaucoma: a newly recognized syndrome. Al-Mayouf SM, Wakil S, Alisamail K. Al Hassnan ZN. *Clin Dysmorphol* 2011 Jan: 20(1) 50-2.
- Novel homozygous mutation in DSP causing skin fragility-woolly hair syndrome: report of a large family and review of the desmoplakin-related phenotypes. Wakeel S, Al-Owain M, Shareef F, Al-Fatani A, Hamadah E, Haider M, Al-Hindi H, Awaji A. Khialifa O, Baz B, Ramadhan R, Meyer B. *Clin Genet*. 2010 Jul 22.

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. The Genetic causes of immunodeficiency are very browed heterogeneous collection of diseases such as severe combined immunodeficiency (SCID), Familial Hemophagocytic Lymphohistiocytosis (FHL), Griscelli syndrome. Hyper IgE, Hyper IgM, Hypogammaglobulinemia, among others. In this regard, we have identified many novel mutations that are implicated as the underlining causes of immunodeficiencies. The other branch of our section is the study of the regulation of the T-Cell receptor alpha and delta (TCRα/δ) gene locus and on the role of RORγT transcription factor in controlling T cell development and its role in protecting us from developing auto-immune diseases and cancer. So far, we have characterized 5 promoter elements within the TCRα/δ locus that control the expression and recombination events during the T cell development within the thymus. In addition, we were able to prevent thymoma development in mice deficient in the RORgT protein by breeding them onto Rag deficient background with rearranged TCRβ transgene implicating Rag protein as the cause of thymoma in the absence of RORγT protein. In the coming year we will continue to define the underlining genetic causes of immunodeficiencies particularly in the cases were all known implicated genes have been excluded. Moreover, we will continue to study the chromatin and transcriptional regulation of the TCRα/δ locus as well as the RORγT particularly in regard to identify interacting partners as described in the RAC-approved research projects.

RAC-APPROVED RESEARCH ACTIVITY

PROJECT TITLE: **Underlying Genetics of Familial Hemophagocytic Lymphohistiocytosis (FLH) in Saudi Arabia**

RAC # 2080 041

INVESTIGATORS: *Dr. Ali Al-Ahmari, Dr. Abbas Hawwari. Dr. Bandar Al Saud, Dr. Ibrahim Al-Fawaz, Dr. Mohab Ayas.*

PROJECT DESCRIPTION AND PROGRESS: Hemphagocytic Iymphohistiocytosis (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. Studies in recent years have revealed the underlying genetic defects in some forms of FHL. These findings have provided an explanation for the defective cytotoxic cell function in FHL. Molecular defects of Saudi patients with FHL are unknown. This study is going to elucidate the genetic defects in this subgroup of patients. Conducting this study is critically needed because of the increasing incidence of the disease due to the high consanguineous marriage rate in Saudi Society. Also knowing the molecular defects in FHL Saudi patients will be of tremendous value in the diagnostic confirmation in symptomatic individuals, screening of the related-bone marrow donors prior to Stem Cell Transplantation, presymptomatic diagnosis of at-risk siblings, identification of carriers, prenatal diagnosis, preimplantation Genetic Diagnosis (PGD) and genetic counseling.

So far we have completed the following study:

NOVEL MOLECULAR CHANGES AND THEIR ASSOCIATED CLINICAL CHARACTERISTICS IN SAUDI PATIENTS WITH FHL

Ali Al-Ahmari, Osama Alsmadi , Lina Elbaik , Tanziel Elamin, Bandar Al-Saud, Saleh Al-Shambri, Moheeb Al-Awwami, Ibrahim Al-Fawaz, Mouhab Ayas, Khawar Siddiqui, Mohammad Viqaruddin and Abbas Hawwari

Familial Hemophagocytic Lymphohistiocytosis (FHL) is a rare autosomal recessive disorder which is characterized by uncontrolled activation of lymphocytes leading to massive lymphohistiocytic infiltration of body organs including central nervous system (CNS).The hallmark of the disease is impaired or absent function of cytotoxic lymphocytes and natural killer cells as a result of several genetic defects. Up to date, four FHL–causing genes have been identified: PRF1, MUNC13-4, and STX11 and STXBP2. The Saudi Arabian population is known to be genetically homogenous due to high consanguinity and the tribal nature of the community. Higher incidence of inherited diseases has been reported in Saudi Arabia. We herein report the novel molecular changes and their associated clinical characteristics in Saudi FHL patients. Saudi patients with the clinical diagnosis of FHL in the period of 1995 through 2011 and available DNA samples were identified. As of now, analysis for PRF1, MUNC13-4, and STX11 and STXBP2 mutations by direct gene sequencing from 40 patients were completed. Twenty-eight patients with ten different novel mutations were identified and their clinical and biochemical profiles were retrospectively captured. Among 40 patients with FHL screened for the above mentioned molecular defects, 28 patients were found to have 10 different novel mutations. One novel STX11 mutation was identified in 7 patients of the same tribe whereas another mutation was identified in 2 related patients with PRFI genetic defect. Additional two novel mutations were identified in 10 patients of 9 unrelated families with STXBP2 gene defect. The remaining 6 novel mutations were identified in 9 patients of 7 unrelated families with Munc13-4 molecular defect. Three previously reported mutations were detected in patients with Munc13-4(two patients) and PRF1 (one patient) genes. No molecular defects were identified in the remaining 9 (23%) patients. The presenting clinical and biochemical features were similar in the various genetic groups. The disease presented in the first year of life in all but 2 patients with STX11 mutations where they presented at 5 and 3 years of age. Parents Consanguinity was observed in 70% of our patients cohort. Two thirds of the Unc13-4 and all PRF1 patients died of disease of progression prior to Stem Cell Transplantation. Four STXBP2

patients with P477L missense mutation died either of disease progression or transplantation-related complications whereas two patients continued to have multiple episodes of disease reactivation after Stem cell transplantation with 9 and 12 years survival. This data shows the high consanguinity rate in Saudi population. Furthermore, majority of mutations in Saudi patients with FHL are novel. Early presentation and disease progression were observed in majority of patients with PRFI and MUNC13-4 mutations. Long term survival was seen in some patients with STXBP2 mutations in spite of multiple mild episodes of disease reactivations post Stem Cell Transplantation.

PROJECT TITLE: **Underlying molecular genetic defects of Primary Immunodeficiency Diseases in Saudi Arabia**

RAC # 2080 025

INVESTIGATORS: *Dr. Hamoud Al-Mousa, Dr. Abbas Hawwari, Dr. Abdulaziz Al-Ghonaium, Dr. Hasan Al-Dhekri, Dr. Saleh Al-Muhsen, Dr. Rand Arnaout, Dr. Bandar Al-Saud.*

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.

So far we have completed work on 4 immunodeficiency diseases that are ready for publication as follow:

GENETIC DEFECTS OF GRISCELLI SYNDROME TYPE 2 IN SAUDI ARABIA

Abbas Hawwari, Abdulaziz Al-Ghonaium, Hasan Al-Dhekri, Saleh Al-Muhsen, Bandar Al-Saud, Rand Arnaout, Safa Al-Hisi, Hamoud Al-Mousa

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.

CLINICAL AND MOLECULAR CHARACTERIZATION OF AUTOSOMAL RECESSIVE HYPER IGE SYNDROME IN SAUDI ARABIA

Abbas Hawwari, Zobaida Alsum, Safa Al-Hisi, Esteban Borrero, Hanif G. Khalak, Nazima Ades, Osama Alsmadi, Rand Arnaout, Abdulaziz Al-Ghonaium, Saleh Al-Muhsen, Hasan Al-Dhekri, Bandar Al-Saud, Hamoud Al-Mousa

Autosomal-recessive hyper-IgE syndrome (AR-HIES) is a combined immunodeficiency characterized by susceptibility to viral infections, eczema and high serum IgE. Mutations in DOCK8 are responsible for many, though not all cases. Further characterization of clinical, immunological and molecular features may improve our understanding of its pathogenesis. Clinical data of 25 patients diagnosed with AR-HIES were collected. Eighteen patients screened for STAT3, Tyk2 and Dock8 mutations. Sinopulmonary infections, dermatitis, hepatic disorders, cutaneous and systemic bacterial, fungal and viral infections were the most common clinical features. Autoimmunity, malignancies and allergies are common complications. Twelve patients died with a median age of 10 years. No consistent immunological findings. Two novel DOCK8 mutations were found in nine patients resulted in stop codons. In addition, 4 patients from two separate families were found with 2 gross deletions. In one family the deletions spanned the entire Dock8 gene and the surrounding genes. In the other family, the deletion extended from somewhere at the tip of chromosome 9 to the middle of DOCK8 gene.. No mutations found in STAT3 or TYK2 genes. Autosomal recessive hyper-IgE disease is a combined immunodeficiency disease characterized by high morbidity and mortality rate. Early consideration of hematopoetic stem cell transplantation might improve the outcome. DOCK8 defect were found in 72% of patients screened. Patients with no identified genetic etiology are likely to carry mutations in the regulatory elements of genes tested or in novel genes that are yet to be discovered.

CLINICAL, IMMUNOLOGICAL, AND MOLECULAR CHARACTERIZATION OF HYPER-IGM SYNDROME DUE TO CD40 DEFICIENCY IN 11PATIENTS

Abbas Hawwari, Zobaida Al-Sum, Hanadi Alassiri, Abdulaziz Al-Ghonaium, Saleh Al-Muhsen, Hasan Al-Dhekri, Rand Arnaout, Osama Alsmadi, Esteban Borrero, Asm'a Abu-staiteh, Hamoud Al-Mousa, Bander K. Al-Saud

Autosomal-recessive hyper-IgE syndrome (AR-HIES) is a combined immunodeficiency characterized by susceptibility to viral infections, eczema and high serum IgE. Mutations in DOCK8 are responsible for many, though not all cases. Further characterization of clinical, immunological and molecular features may improve our understanding of its pathogenesis. Clinical data of 25 patients diagnosed with AR-HIES were collected. Eighteen patients screened for STAT3, Tyk2 and Dock8 mutations. Sinopulmonary infections, dermatitis, hepatic disorders, cutaneous and systemic bacterial, fungal and viral infections were the most common clinical features. Autoimmunity, malignancies and allergies are common complications. Twelve patients died with a median age of 10 years. No consistent immunological findings. Two novel DOCK8 mutations were found in nine patients resulted in stop codons. In addition, 4 patients from two separate families were found with 2 gross deletions. In one family the deletions spanned the entire Dock8 gene and the surrounding genes. In the other family, the deletion extended from somewhere at the tip of chromosome 9 to the middle of DOCK8 gene.. No mutations found in STAT3 or TYK2 genes. Autosomal recessive hyper-IgE disease is a combined immunodeficiency disease characterized by high morbidity and mortality rate. Early consideration of hematopoetic stem cell transplantation might improve the outcome. DOCK8 defect were found in 72% of patients screened. Patients with no identified genetic etiology are likely to carry mutations in the regulatory elements of genes tested or in novel genes that are yet to be discovered.

NOVEL ZAP70 MUTATIONS CAUSING SEVERE COMBINED IMMUNODEFICIENCY DISEASE IN SAUDI ARABIA

Abbas Hawwari, Osama Alsmadi, Hasan Al-Dhekri, Abdulaziz Al-Ghonaium, Saleh Al-Muhsen, Bandar Al-Saud, Rand Arnaout, Hamoud Al-Mousa

SCID with selective CD8 deficiency is a very rare type of SCID typically caused by defects in ZAP70 (ζ-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 deficiency were screened for mutation 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.

PROJECT TITLE: **Transcriptional Regulation of TCRα/δ Locus**

RAC # 2080 019

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

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 TCRα/δ locus is active in double negative (DN) stage of T cell development only which results in the rearrangements of this gene segments to generate TCRδ 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 TCTα 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 bread this mouse onto the Rag deficient background with or without TCRβ 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: **RORγt Role in T Cell Development, Autoimmunity and Transformation**

RAC # 2080 046

INVESTIGATORS: *Dr. Abbas Hawwari, Dr. Namik Kaya, Dr. Dilek Colak, Dr. Goran Matic.*

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

Saudi Newborn Screening [NBS] Program for Metabolic Diseases

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PROJECT DESCRIPTION

The National Newborn Screening is a public health program implemented to detect and prevent selected congenital and heritable disorders. These disorders cause severe mental retardation, illness, or death if not treated early in life. Numerous studies showed that early detection and early intervention may prevent these consequences.

1. Phenylketonuria (PKU)
2. Maple Syrup Urine Disease (MSUD)
3. Arginosuccinase Deficiency (ASL)
4. Citrullinemia (ASD)
5. HMG-CoA Lyase Deficiency (HMG)
6. Isovaleric Acidemia (IVA)
7. Methylmalonic Acidemia (MMA)
8. Propionic Acidemia (PA)
9. Beta-ketothiolase Deficiency (BKT)
10. Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)
11. Glutaric Acidemia type-I (GA-I
12. Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
13. Galactosemia (GAL)
14. Congenital Hypothyroidism (CH)
15. Congenital adrenal Hyperplasia (CAH)
16. Biotinidase Deficiency (BD)

PROGRESS: In 2011, Prince Salman Center for Disability Research (PSCDR) continued to execute the strategy for National Newborn Screening Program (NNSP) in partnership with Ministry of Health (MOH). The main goal is to screen more than three hundred thousand (300,000) newborns per year. The program is supervised and financed by the MOH and administered by PSCDR. As a result of this strategy, more than hundred hospitals were participated in this expansion during 2011. Besides the tests, PSCDR provided medications and special formulas to twenty-four (24) MOH treatment centers. PSCDR develops and maintains the NNPS database which allows the health care providers to access and observe their result via a secured WEB portal. The National Laboratory of Newborn Screening (NLNBS) managed to screen more than a hundred and twenty thousand babies from the participated hospitals and thousands of specialized diagnostic assays. In total, the Laboratory performed about seven hundred thousand (700,000) different tests in 2011. One hundred and thirty four (134) babies were found to be affected this year, yielding a total of six hundred and thirty eight (638) affected newborn being detected since the start of the program. The incidence for the sixteen (16) screened diseases was 1:1000. PSCDR is currently working closely with the MOH and other health care providers to execute the expansion of the program to cover the screening of three hundred thousand (300,000) newborns in 2011-2012.

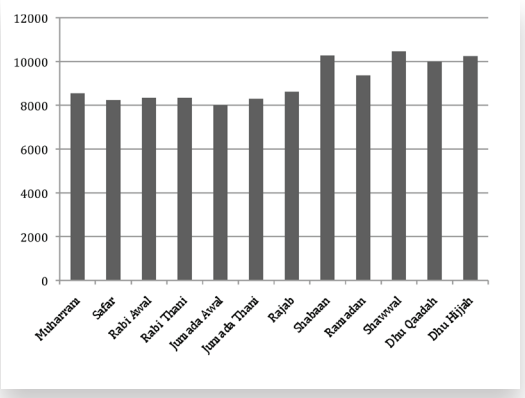

Figure1: Total statistics for the Newborn Screening Program 2011

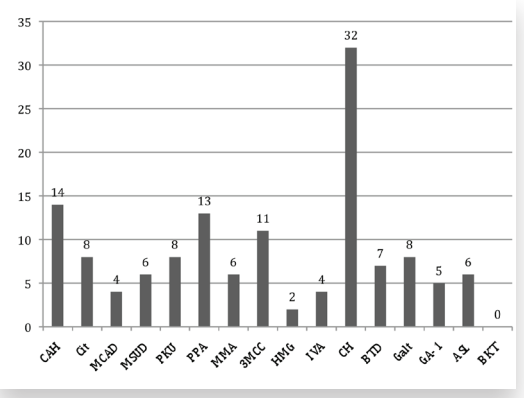

Figure 2 Total numbers of detected abnormal cases by NBS (Year 2011)

QUALITY ASSURANCE AND PROFICIENCY TESTING AT NLNBS

The National Laboratory for Newborn Screening (NLNBS) serving the most precious customers in any nation; and they are its newborns. Because of this, NLNBS established its' tailored quality assurance program which is a comprehensive process that should involve all elements of a successful clinical laboratory. As such, quality assurance at NLNBS encompasses personnel qualifications and work quality; policies and procedures for human resources and analytical aspects; equipment maintenance, performance and upgrade; and quality control and documentation throughout the pre-analytical, analytical, and post analytical stages of samples analysis.

Laboratory Proficiency Testing (PT) is an indispensable component in a laboratory quality assurance plan. The aim of Proficiency Testing is to enhance the capability and to demonstrate competence of the laboratory. PT is an inter-laboratory assessment tool and a powerful quality assurance device that permits laboratories to examine their performance and balance their results against similarly functioning laboratories. Regulations of the Clinical Laboratory Improvement Act (CLIA) and the Joint Commission (JC) , and guidelines of the Association of Public Health Laboratories (APHL) require clinical laboratories to maintain successful performance on PT. There is a rising demand from regulatory bodies and laboratory customers for independent verification of laboratory quality and competency through an external type of PT; where samples are sent from an external body. Acknowledging these demands and because NLNBS is serving the most precious customers in any nation; and that is its newborns; the Laboratory participates in two external proficiency testing programs.

NLNBS is a member of the Center for Disease Control (CDC) and Newborn Screening Quality Assurance Program (NSQAP) since 2004. The newborn screening sections of NLNBS are a part of the PT and Quality Control (QC) testing sectors of the NSQAP. PT testing is performed three times per year and QC testing is done two times a year. The confirmatory section of NLNBS is a member of the European Research Network for Evaluation and Improvement of screening, Diagnosis and Metabolism (ERNDIM) Quality Assurance Program since mid 2005.

ESTABLISHMENT OF A NEWBORN SCREENING DATABASE AND WEB PORTAL

In an effort to facilitate and expedite transmittal of information about screening test results of the newborn screening program to the participating hospitals aiming at early management of affected cases, a database and web portal has been established by the PSCDR.

This web portal is a secured entity and password protected; it allows the designated users to view the test results for screened babies at their hospital or facility. The portal brings the results from the National Newborn Screening Program (NNSP) database, and displays it on portal pages.

The clinical and administrative coordinators at the participating hospitals were provided with the required user names and passwords. In addition the MOH were supplied with twenty-five (25) wireless connect devices to enable the treatment centres to connect to the internet from any place regardless of availability of other internet connections. The view is limited to each hospital samples to preserve confidentiality of other hospitals samples. The participating hospitals will be provided with personal computers, fax machines, and printers to optimize their effectiveness in the program execution. Other Ministry of Health hospitals that may join the program at any time may benefit from these facilities.

FUTURE PLANS

The future plan is to expand the features of this web portal, and for this purpose, a committee has been formed to explore possibilities of sorting the screening result data, and produce other statistical reports as to the number of tested cases, number of positive tests, number of abnormal tests, type of abnormal etc., sorted by single hospital and / or all hospitals. The members of the committee are assigned from both MOH and PSCDR.

Saudi Diagnostics Laboratory

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Saudi Diagnostic Laboratories (SDL) applies the translational Research Programs of the Department of Genetics for the provision of molecular diagnostic services for patient care. In particular, during 2011 SDL grew considerably in the areas of prenatal testing and carrier screening. The laboratory is fully accredited by the College of American Pathologists and focuses its diagnostic activities on inherited disorders. SDL is a reference for many inherited disease including Inborn Errors of Metabolism where it has identified and provides a diagnostic service for Arab specific mutations. As a consequence the repertoire of genes/mutations for which clinical diagnostic services are offered continues to grow.

SDL performs a repertoire of over 200 tests many of which are unique to its operation. Through these activities the KFSH&RC is becoming increasingly independent in molecular genetic testing. Animal genetics is a significant component of services offered by SDL. This is now a mature service dealing with an excess of 1,000 samples per year for parentage verification of Arabian horses. This s is central to the registration of these valuable animals. SDL is fully recognized for this purpose by the World Arabian Horse Organization (WAHO) and is a member of the International Society for Animal Genetics.

SDL provides diagnostic services for many clinical departments and sections at KFSH&RC. These include Medical Genetics, Pediatrics, Neurosciences, Obstetrics and Gynecology, Pediatric Immunology and Pediatric Nephrology among others. During 2011 over 2000 diagnostic tests were performed by SDL in support of these services. The list of external clients for SDL has also grown during 2011. SDL worked closely with the Department of Pathology and Laboratory Medicine and is moving towards integrating its Quality Control and Accreditation activities with DPLM.

Preventative medicine through carrier detection, pre-implantation genetic diagnosis and prenatal testing is a major service activity of SDL. Prenatal testing is a regular part of the SDL workflow with over 200 cases having been processed in 2011. SDL is working closely with the Research laboratories of the Department of Genetics to advance capabilities in prenatal testing through an externally funded KACST project for SAR 2 million over 2 years.

Sequencing Core Facility

HEAD
Dorota Monies, PhD

MEMBERS
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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 45- 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 Analyzer. The ABI 3730xl uses a capillary electrophoresis system that creates a sensitive detection system, long sequence reads (up to a 1000 bases for high quality DNA), short run times, and low operating/reagent costs. The ABI 3730xl DNA Analyzer is an automated system (sample loading, separation matrix preparation, and sequence analysis) which coupled with the facility's liquid handling robot, dramatically reduces the introduction of human error.

SERVICES OFFERED

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

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

Objective Quality Controls
The facility places 2 controls on each sequencing plate. The controls consist of one negative and one positive controls. The negative controls consist of water being added to the sequencing reaction instead of DNA template. This control detects proper sequencing reaction plate setup, purity of the water used in the sequencing reactions, and any cross-contamination between the 96 wells of the reaction plate. The positive controls consist of M13 primers being used to sequence pGEM 3Zf(+).

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.

Subjective Quality Controls
All sequences are reviewed by trained staff in the DNA Sequencing Facility. A sequence reaction is considered successful if the sequence contains high quality base calls for at least 90% of the first 700 bases. If the sequence fulfills the above criteria and the negative/positive plate controls pass the set quality criteria, the sequence is released to the investigator. If a sequence fails the subjective quality control, the sequence is investigated with troubleshooting and "redo" policy.

ADDITIONAL SERVICES

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.

Oligo orders
We cooperate with *Metabion International AG* from Germany which offers a complete spectrum of custom oligos - from high quality/high throughput oligos (MTP formats) to high-quality special oligos like Real-time PCR probes including LightCycler® probes.Custom DNA Primers and Probes are available as standard deoxynucleotides, modified bases, 5' modified nucleotides, S-oligos for antisense studies. They are available in different scales: 3 standard scales for dual labelled fluorogenic probes, some single labelled DNA-oligonucleotides, and S-oligos; 4 standard scales for unmodified oligos, and most

single labelled DNA-oligonucleotides and 7 standard scales for LightCycler® probes. A comprehensive Synthesis Report comes along with each order, indicating oligo name and sequence, composition of bases, synthesis scale and yield in ODs, µg and nmol, delivery mode (lyophilized or liquid), primer concentration, molecular weight, melting temperature, GC%, purification mode and quality control.

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 71 researches within the Research Center and also from outside e.g. the King Saud University. In last year we generated approximately 20,000 genotyping results and 400,000 sequencing reads.

HUMAN CANCER GENOMIC RESEARCH

HUMAN CANCER GENOMIC RESEARCH

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The mission of Human Cancer Genomic Research (HCGR) is to conduct translational research on cancers that are more prevalent in the Kingdom of Saudi Arabia. The main focus of the Research Centre is to perform high quality translational research using state of the art technology including HiSeq Illumina Sequencer, Affymetrix, tissue micro array & high throughput sequencing analyzer. The main goal of this department is also to design better strategies to diagnose, prognosticate & treat neoplasms that are specifically relevant to Saudi Arabia as compared to the Western population.

As a part of global consortium, we have launched a new project from Saudi Arabia to identify the genomic drivers in thyroid cancer, which will improve understanding and clinical management of this disease. The International Cancer Genome Consortium (ICGC) has a decade-long goal to generate high-quality genomic data on more than 25,000 tumors for up to 50 types of cancer that are of clinical and societal importance across the globe.

In the year 2011, we were able to continue and complete many ongoing projects that were initiated in the previous years. Previously, we have identified many molecules that can either be used as diagnostic or prognostic markers or can be targeted therapeutically with small molecular peptides as new treatment strategy for the management of these cancers. One prime example is of FoxM1 gene that was found to be over-expressed in colo-rectal carcinoma (CRC) and was found to have an adverse prognostic effect on CRC patients. We expanded our studies to study the expression status of FoxM1 in other cancer and we found that FoxM1 was over-expressed in diffuse large B-cell lymphoma (DLBCL) and papillary thyroid cancer (PTC). Furthermore, we were able to target the expression on this gene using either specific inhibitors or siRNA strategy targeted against FoxM1 gene *in vitro* and found that down-regulation of FoxM1 led to inhibition of cell viability and induction of apoptosis in a dose dependent manner. FoxM1 down-regulation also led to inhibition of migratory and invasive property of the cancer cell, there by making it less aggressive. Another example is the c-Met gene and its activated form, p-Met that was found to be over-expressed in CRC and DLBCL samples. We expanded our study and found that p-Met was also found to be over-expressed in 69.9% of PTC and targeting activated c-Met can be achieved using specific inhibitors against c-Met. We have also started generating promising sequencing data using the recently acquired HiSeq sequencer from Illumina that may help in identifying genes that may be playing a role in pathogenesis of various cancers of Saudi origin. With this technique, new avenues of cancer research will be explored and this will improve the diagnostic and prognostic criteria of cancer. In addition, this may also improve the therapeutic modalities of these cancers by identifying new targets for intervention.

We were able to publish 15 full length articles in reputable peer-reviewed scientific journals. Integration of three major components of our laboratory studies, (*i*) Clinical Research using tissue microarray as well as patient's clinical history, (*ii*) *in vitro* studies using cell lines to study the functional aspects of these cancers and finally correlating these findings (*iii*) *In vivo* using either SCID or Nude mice has greatly improved our chances in better understanding the underlying patho-physiology of cancer. This combined approach has definitely enhanced and improved the chances of treating these cancers using targeted therapy against certain genes that are being discovered with the help of these techniques.

We hope to continue with our research activities in the same fervor and enthusiasm to make 2012, even more productive than last year.

Human Cancer Genomic Research is further divided into 3 closely inter-related sections.

- Experimental Molecular Pathology
- Molecular Oncology
- Biological Repository Center

EXPERIMENTAL MOLECULAR PATHOLOGY

In the year 2011, HCGR has been able to identify several genes that were found to be important in the pathogenesis of various cancers. These genes included MTOR that was found to be over-expressed in ovarian cancer and diffuse large B-cell lymphoma (DLBCL). In addition we also found that mToR expression is associated with other proteins that render cancers to be more aggressive and lethal.

MOLECULAR ONCOLOGY

This department focuses mainly on translational studies, towards developing diagnosis or therapeutic strategies in improving the management of cancer. This is a unique facility and provides unprecedented tools for translational research in the region.

mToR has been found to be dysregulated in various cancers. In this section, we were able to target MTOR using either pharmacological inhibitors such as Torin 2 or siRNA knockdown strategies to inhibit cell growth and induce apoptosis in ovarian cancer and DLBCL cell lines. Further studies are being conducted to determine the role of MTOR in the pathogenesis of these cancers. We will further confirm these findings *in vivo* by inoculating tumor

cells in either SCID or Nude mice and then treat them with the specific inhibitors and follow the progress of these tumors over several weeks.

BIOLOGICAL REPOSITORY CENTRE

The main stay of the biological repository centre (BRC) is the proper preservation & storage of archival frozen tumor and normal tissue samples. DNA and RNA extracted from these frozen samples are being utilized for mutational analysis and differential expression studies in various projects.

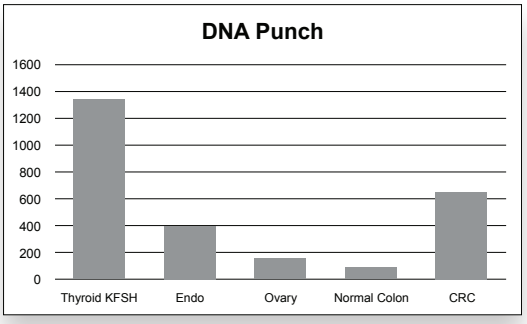
Tasks

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

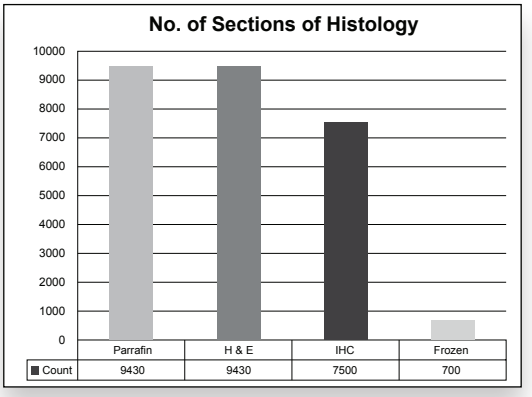
Activities

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 6222 specimens were processed in the year 2011–2012. Five to ten DNA punches obtained for each tumor specimen.

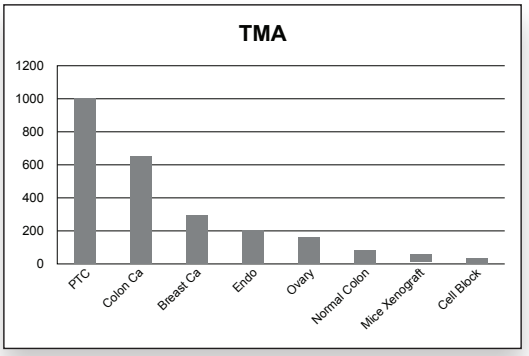


2. Cell blocks prepared from cell lines used for immunohistochemistry–57.
3. Commercial cell lines acquired from ATCC and other biorepository centers expanded and grown in bulk over 700 vials frozen and stored in liquid nitrogen.



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.
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.

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 2,137 tumor and normal tissue specimens were arrayed in a TMA format in year 2011–2012. Six to ten TMA replicas obtained for each tumor specimens. In addition we have 3 cell line block TMA.



RESEARCH PROJECTS

Approved Projects Funded by KACST/NCPST:
1. RAC 2080 031 - Role of c-MET in Saudi Arabian Papillary Thyroid Carcinoma for Novel Therapy.
2. RAC 2080 030 - Prognostic Significance of Genetic Alterations in Saudi Colorectal Cancers.
3. RAC 2080 029 - Cyclooxygenases: Target for Epithelial Ovarian Cancer Prevention and Treatment.

RAC Active Projects:
1. RAC 2060 008 - Molecular Signatures of Diffuse Large B-cell Lymphoma (DLBCL), Lung and Ovarian Cancer: A Pilot Study.
2. RAC 2040 004 - Molecular Signatures of Cancer; Clinical Significance in Saudi Arabian and European Cancer Patients.

RAC Completed Projects:
1. RAC 2070 004 - Role of PI3-kinase-AKT Pathway in Epithelial Carcinomas.
2. RAC 2040 014 - Role of JAK/STAT and PI3-Kinase Pathways in Hematological Malignancies.
3. RAC 2090 012 (SANAD Project) - Real-time PCR Assay of Terminal Deoxynucleotodyl Transferase (TdT) for detection of acute lymphoblastic-leukemia in cerebrospinal fluid.
4. RAC 2050 015 - Translational initiatives in Hematological malignancies.

Human Cancer Genomic Research is actively involved in programs relating to four different organ sites:

- Hematological Malignancies
- Thyroid
- Colon
- Ovary

HEMATOLOGICAL MALIGNANCIES

PROJECT TITLE: **Over-expression of FoxM1 offers a promising therapeutic target in diffuse large B-cell lymphoma**

INVESTIGATORS: *Khawla S. Al-Kuraya, Shahab Uddin, Prashant P. Bavi, Maqbool Ahmed, Abdul K. Siraj, Rong Bu, Azhar R. Hussain, Zeenath Jehan*

DESCRIPTION

BACKGROUND: FoxM1 has been shown to play a critical role in pathogenesis of various epithelial malignancies. However, its role in lymphoid malignancies is not fully elucidated. We therefore investigated the role of FoxM1 expression in a large cohort of diffuse large B-cell lymphoma samples and panel of cell lines.

DESIGN AND METHODS: FoxM1 expression was investigated in a large series of diffuse large B-cell lymphoma tissues in a tissue micro array format by immunohistochemistry. Apoptosis was measured by flow cytometry and protein expression was detected by immuno-blotting using diffuse large B-cell lymphoma cell lines following treatment with either pharmacological inhibitor of FoxM1 or small interference RNA knockdown strategy. Invasion/Migration and soft agar colony assays were also performed following treatment with FoxM1 inhibitor.

RESULTS: FoxM1 expression was detected in 84.6% of diffuse large B-cell lymphoma tumors and found to be significantly associated with proliferative tumor marker Ki67 (p<0.0001), matrix metalloproteinases-2 (p=0.0008), matrix metalloproteinases-9 (p=0.0002), S-phase kinase associated protein-2 (p<0.0001) and inversely associated with p27 expression (0.0215). Expression of small interference RNA targeted against FoxM1 or treatment of diffuse large B-cell lymphoma cells with thiostrepton caused its down-regulation accompanied by decreased expression of matrix metalloproteinases-2 and matrix metalloproteinases-9. Inhibition of FoxM1 in diffuse large B-cell lymphoma cells also decreased the invasive and migratory capability and induced caspase dependent apoptosis via activation of mitochondrial apoptotic pathway. Finally, combination of thiostrepton and Bortezomib at sub-toxic doses led to efficient apoptosis in diffuse large B-cell lymphoma cells.

CONCLUSION: Altogether, these results suggest that FoxM1 is over-expressed in a majority of diffuse large B-cell lymphoma samples. These data also indicates that targeting FoxM1 signaling can serve as a potential therapeutic modality in the management of diffuse large B-cell lymphoma.

PROGRESS: Manuscript accepted for publication in Haematologica 2012.

PROJECT TITLE: **The biological and clinical impact of inhibition of NF- κB initiated apoptosis in diffuse large B-cell lymphoma (DLBCL)**

INVESTIGATORS: *Khawla S. Al-Kuraya, Shahab Uddin, Azhar R Hussain, Maqbool Ahmed, Rong Bu, Saeeda O Ahmed, Zeenath Jehan, Prashant Bavi*

DESCRIPTION: NF-κB is frequently over-expressed in a variety of non-Hodgkin's lymphomas (NHLs) and has been implicated in lymphomagenesis; however, its role in diffuse large B cell lymphoma (DLBCL) as a prognostic biomarker has not been fully elucidated. Therefore, we investigated the role of NF-κB and its association with clinicopathological features in a tissue microarray cohort of 230 DLBCL patient samples. We then elucidated the role of NF-κB inhibition on cell viability and apoptosis *in vitro*, using DLBCL cell lines. Using immunohistochemistry, NF-κB was detected in 25.6% (52/203) DLBCL tumours, was associated with activated B cell (ABC) phenotype (p = 0.0054), Epstein-Barr virus (EBV; p = 0.0080) and over-expression of the anti-apoptotic marker XIAP (p = 0.0013). DLBCL cases with nuclear expression of NF-κB showed a significantly poorer overall survival as compared to those without NF-κB expression (p = 0.0236). In a multivariate analysis using a Cox proportional hazard model for IPI and NF-κB expression, the relative risk was 2.97 for high NF-κB expression (95% CI 1.27–6.94; p = 0.0113) and 7.55 for the high-IPI group (95% CI 3.34–18.35; p < 0.0001). *In vitro*, Bay 11–7085 inhibited constitutively active NF-κB expression in a dose-dependent manner and inhibition of NF-κB also down-regulated expression of the downstream target gene products Bcl-2, Bcl-XL (BCL2L1), XIAP and Survivin, leading to apoptosis via activation of the mitochondrial apoptotic pathway. NF-κB over-expression was found to be an independent prognostic marker for poor survival in DLBCL. Altogether, these results suggest that NF-κB may be a useful prognostic biomarker and a potential target for therapeutic intervention in DLBCL.

PROGRESS: Manuscript published in Journal of Pathology 2011.

THYROID CANCER

PROJECT TITLE: **FoxM1 and its association with Matrix Metalloproteinase signaling pathway in papillary Thyroid Carcinoma**

INVESTIGATORS: *Khawla S. Al-Kuraya, Shahab Uddin, Abdul K. Siraj, Azhar R Hussain, Maqbool Ahmed, Prashant P. Bavi, Jehad Abubaker, Zeenath Jehan.*

CONTEXT: FoxM1 transcription factor has been shown to promote pathogenesis of several malignancies. FoxM1 has also been shown to be associated with Matrix metalloproteinases (MMP) in various cancers. However, little is known about its function in papillary thyroid carcinoma (PTC).

OBJECTIVE: In this study, we investigated the role of FoxM1 in pathogenesis in a large series of PTC in a tissue microarray format followed by *in vitro* and *in vivo* studies using PTC cell lines and nude mice.

DESIGN: Expression of FoxM1 and its associated proteins were investigated in Middle Eastern PTC samples by Immunohistochemistry. Apoptosis was measured by flow cytometry and immuno-blotting. Invasion and migration studies were performed using 8 micron transwell plates.

RESULTS: FoxM1 was over expressed in 28.4% of PTC and significantly associated with activated MMP-9 (p=0.0004), XIAP (p=0.0024), and Bcl-XL (p=0.0014) expression. Treatment of PTC cell lines with thiostrepton; an inhibitor of FoxM1 resulted in inhibition of cell viability via induction of apoptosis. In addition, thiostrepton treatment of PTC cells or expression of FoxM1 specific siRNA down-regulated expression of FoxM1 accompanied with decreased MMP-2 and MMP-9 expression. Furthermore, inhibition of FoxM1 attenuated migration and invasion of PTC cells. Interestingly, over-expression of FoxM1 rescued the effects of thiostrepton in PTC cell lines. Finally, treatment of PTC cell line xenografts with thiostrepton resulted in growth inhibition of tumors in nude mice via downregulation of FoxM1 and MMP-9 and MMP-2.

CONCLUSION: Altogether, this is the first study showing that FoxM1 and its associated signaling pathway play a critical role in the pathogenesis of PTC and may be a potential target for therapeutic intervention for treatment of these cancers.

PROGRESS: Manuscript Published in *J Clin Endocrinol Metab* Epub 2011 Nov 2

PROJECT TITLE: **c-Met inhibitor synergizes with tumor necrosis factor-related apoptosis-induced ligand to induce Papillary Thyroid Carcinoma cell death**

INVESTIGATORS: *Khawla S. Al-Kuraya, Rong Bu, Azhar R. Hussain, Maqbool Ahmed, Prashant Bavi, Saif Al-Deen Suliman Alsobhi, Abdurahman Al-Nuaim, Shahab Uddin*

DESCRIPTION: The Met receptor tyrosine kinase is overexpressed and/or activated in variety of human malignancies. Previously we have shown that c-Met is overexpressed in Middle Eastern Papillary Thyroid Carcinoma (PTC) and significantly associated with aggressive phenotype, but its role has not been fully elucidated in PTC. The aim was to deteremine the functional link between c-Met/AKT signaling pathway and Death Receptor 5 (DR5) in a large cohort of PTC in a tissue microarray format followed by functional studies using PTC cell lines and Nude mice. Our data show that high expression of p-Met and DR5 were significantly associated with aggressive phenotype of PTC. Treatment of PTC cell lines with PHA665752, an inhibitor of c-Met tyrosine kinase, inhibited cell proliferation and induced apoptosis via mitochondrial pathway in PTC cell lines. PHA665752 treatment or expression of c-Met siRNA resulted in dephosphorylation of c-Met, AKT and its downstream effector molecules. Furthermore, PHA665752 treatment up-regulated DR5 expression via generation of Reactive Oxygen Species (ROS) in PTC cell lines, and synergistically potentiated death receptor-induced apoptosis with TRAIL. Finally, co-treatment with PHA665752 and TRAIL caused more pronounced effect on PTC xenograft tumor growth in Nude mice. Our data suggest that c-Met/AKT pathway may be a potential target for therapeutic intervention for treatment of PTC refractory to conventionally therapeutic modality.

PROGRESS: Manuscript published in Mol Med. 2011 November

COLON

COLORECTAL CARCINOMA

PROJECT TITLE: **Co-expression of Activated c-Met and Death Receptor 5 predict a Better Survival in Colorectal Carcinoma**

INVESTIGATORS: *Khawla S. Al-Kuraya, Shahab Uddin, Prashant P. Bavi, Zeenath Jehan, Azhar R. Hussain, Maqbool Ahmed*

DESCRIPTION: Dysregulated over-expression of hepatocyte growth factor and its receptor, c-Met

has been reported in various cancers. However, its role in colorectal carcinoma (CRC) has not been elucidated. Therefore, we investigated the role of p-Met in Middle Eastern CRC patient samples and cell lines. p-Met was over-expressed in 80.8% of CRC and strongly associated with expression of p-AKT (p=0.0219), DR5 (p=0.0344) and Ki67 (p=0.0382) by immunohistochemistry. Co-expression of p-Met and DR5 was seen in 53.1% CRC cases and was associated with less aggressive phenotype characterized by a histology subtype of adenocarcinomas (p=0.0083), well differentiated tumors (p=0.0003) and was an independent prognostic marker for better overall survival (p=0.0064). PHA665752, a selective p-Met inhibitor, induced apoptosis in CRC cells via inactivation of c-Met and AKT. PHA665752 treatment also caused up-regulation of DR5 via generation of ROS and combination treatment with TRAIL and PHA665752 induced significant apoptosis. *In vivo*, co-treatment of CRC xenograft with PHA665752 and TRAIL significantly reduced tumor volume and weight. These data demonstrate a significant correlation between p-Met and DR5 in CRC patients. Furthermore, inhibition of p-Met signaling by PHA665752 in combination with TRAIL significantly inhibited cell growth and induced apoptosis in CRC cell lines suggesting that this may have significant clinical implications as a therapeutic target in treatment of CRC.

PROGRESS: Manuscript published in American Journal of Pathology, December 2011.

PROJECT TITLE: **Bortezomib stabilizes mitotic cyclins and prevents cell cycle progression via inhibition of UBE2C in Colorectal Carcinoma.**

INVESTIGATORS: *Khawla S. Al-Kuraya, Shahab Uddin, Maqbool Ahmed, Azhar Hussain, Nasser Al-Sanea, Alaa AbdulJabbar, Luai H. Ashari, Samar Alhomoud, Fouad Al-Dayel, Zeenath Jehan, Prashant Bavi, Abdul Khalid Siraj*

DESCRIPTION: Substantial evidence implicates the ubiquitin-conjugating enzyme E2C (UBE2C) gene, in several human cancers, including colorectal carcinoma (CRC). We therefore investigated the prognostic value of UBE2C alterations in CRC and UBE2C signaling in CRC cell lines. UBE2C protein expression and UBE2C gene copy number were evaluated on clinical samples by immunohistochemistry and fluorescence *in situ* hybridization in a TMA format. The effect of the proteasome inhibitor bortezomib and small-interfering RNA knockdown was assessed by apoptotic assays and immunoblotting. UBE2C dysregulation was associated with proliferative marker Ki-67, accumulation of cyclin A and B1, and a poor overall survival. UBE2C expression was an independent prognostic marker in early-stage (I and II) CRC. UBE2C depletion resulted in suppression of cellular growth and accumulation of cyclin A and B1. *In vitro*, bortezomib treatment of CRC cells caused inhibition of cell viability via down-regulation of UBE2C. UBE2C knockdown by bortezomib or transfection with specific small-interfering RNA against UBE2C also caused cells to be arrested at the G2/M level, leading to accumulation of cyclin A and cyclin B1. *In vivo*, a significant reduction in tumor volume and weight was noted in mice treated with a combination of subtoxic doses of oxaliplatin and bortezomib compared with treatment with oxaliplatin or bortezomib alone. Altogether, our results suggest that UBE2C and the ubiquitin-proteasome pathway may be potential targets for therapeutic intervention in CRC.

PROGRESS: Manuscript published in American Journal of Pathology, May 2011.

EPITHELIAL OVARIAN CARCINOMA

PROJECT TITLE: **Over Expression of Fatty Acid Synthase in Middle Eastern Epithelial Ovarian Carcinoma Activates AKT and its Inhibition Potentiates Cisplatin Induced Apoptosis**

INVESTIGATORS: *Khawla S. Al-Kuraya, Shahab Uddin, Maqbool Ahmed, Jehad Abubaker, Abdul Khalid Siraj, Prashant P. Bavi, Zeenath Jehan, Azhar R. Hussain*

DESCRIPTION: Fatty Acid Synthase (FASN), the enzyme responsible for *de novo* synthesis of fatty acids has been shown to be deregulated in several cancers including epithelial ovarian carcinoma (EOC). In this study, we investigated the function of FASN signalling pathway in a large series of Middle Eastern EOC patient samples, a panel of cell

lines, and nude mouse model. Using immunohistochemistry, we detected over expression of FASN in 75.5% (114/151) tumor samples. Overexpression of FASN was significantly associated with tumor proliferative marker Ki-67 (p=0.0009), activated AKT (p=0.0117) and XIAP (p=0.0046). Treatment of EOC cell lines with C-75 a selective inhibitor of FASN caused inhibition of EOC cell viability via induction of apoptosis. Inhibition of FASN by C-75 led apoptosis involving the mitochondrial pathway. FASN inhibition caused down regulation of activated AKT and its down stream targets. In addition, inhibition by FASN siRNA caused downregulation of FASN and activation of caspases suggesting the role of FASN in C-75 mediated apoptosis. Furthermore, treatment of EOC cells with subtoxic doses C-75 augmented the effect of cisplatin mediated induction of apoptosis. Finally, treatment of EOC cell line xenografts with combination of C-75 and cisplatin resulted in growth inhibition of tumors in nude mice through downregulation of FASN and activation of caspases. Altogether, our results show overexpression of FASN in Middle Eastern EOC suggesting that FASN may be a potential therapeutic target in a subset of EOC, alone or in combination with other conventional chemotherapeutic agents.

PROGRESS: Manuscript published in Molecular Medicine, 2011.

PROJECT TITLE: **HGF/c-Met pathway plays a prominent role in mediating antiapoptic signals via AKT in epithelial ovarian carcinoma**

INVESTIGATORS: *Khawla S. Al-Kuraya, Zeenath Jehan, Shahab Uddin, Maqbool Ahmed, Azhar Hussain, Thangavel Saravanan, Fouad Al-Dayel, Prashant Bavi*

DESCRIPTION: The Met receptor tyrosine kinase and its ligand, hepatocyte growth factor (HGF), are overexpressed and/or activated in a variety of human malignancies. However, its role in epithelial ovarian carcinoma (EOC) has not been clearly elucidated. Therefore, we investigated the role of HGF/c-Met signaling pathway in a large series (156) of Saudi EOC patient samples, a panel of cell lines, and xenografts in a NUDE mouse model. Using immunohistochemistry, c-Met overexpression was found in 27.2% Middle Eastern EOC samples and was associated with an advanced tumor stage (P=0.0187). c-Met overexpression was also associated with antiapoptotic markers X-chromosome-linked inhibitors of apoptosis (XIAP) (P=0.0008) and Bcl-XL (P=0.0493) expression. Treatment of EOC cell lines with PHA665752 causes a dose-dependent inhibition of cell viability and induction of apoptosis. Furthermore, PHA665752 treatment causes dephosphorylation of AKT and downregulation of antiapoptotic proteins XIAP and Bcl-XL. In addition, PHA665752-induced apoptosis occurs through activation of Bax-mediated release of cytochrome c and activation of caspases. Finally, co-treatment of EOC with PHA665752 and cisplatin causes augmented effect on apoptosis of EOC cells and resulted in synergistic inhibition of EOC xenograft tumor growth in NUDE mice. These results indicate that c-Met/HGF pathway may be a potential target for therapeutic intervention for treatment of EOC.

PROGRESS: Manuscript published in Lab Investigation January 2011.

PROJECT TITLE: **The International Cancer Genome Consortium (ICGC)—Identification of Molecular Significance of Papillary Thyroid Cancer Using Next Generation Sequencing Technology**

As a part of global consortium, we have launched a new project from Saudi Arabia to identify the genomic drivers in thyroid cancer, which will improve understanding and clinical management of this disease. The International Cancer Genome Consortium (ICGC) has a decade-long goal to generate high-quality genomic data on more than 25,000 tumors for up to 50 types of cancer that are of clinical and societal importance across the globe.

Although papillary thyroid cancer constitutes a significant health burden in Saudi Arabia, it is a poorly understood tumor and this tumor type is largely under- researched. Thyroid cancer is the most common endocrine malignancy and differentiated thyroid cancer (DTC), which includes papillary (PTC) and follicular (FTC) subtypes, accounts for 90% of all thyroid malignancies In Saudi Arabia, thyroid cancer

ranked second only to breast cancer among females, eleventh among males and this increased incidence is prevalent in other Gulf Council Countries (GCC) also. Most patients with DTC do well with traditional therapy which includes total thyroidectomy, radioiodine ablation (RAI) and thyroid hormone suppression. However, some will go on to develop progressive disease that is not amenable to further surgery and/or not responsive to RAI. Currently, there are no clinical or molecular diagnostic tools to predict recurrence and aggressiveness of a subset of PTC. We aim to analyze the genomic DNA sequences of 500 thyroid cancers and the corresponding DNA from blood. With the goal of a better understanding the pathobiology of thyroid carcinogenesis we will use state of the art "deep sequencing" technology to decipher the molecular and genetic signature of Saudi PTC. The development of next-generation (NextGen) sequencing technologies has spurred high hopes for the identification of novel biomarkers for disease diagnosis, prognosis, and prediction, including thyroid cancer. Our objectives will be achieved through the following aims: the studies of specific aim 1 will be the generation of comprehensive catalogues of genomic abnormalities (somatic mutations) in thyroid cancer of the papillary thyroid carcinoma histology subtype which is of clinical and social importance in Saudi Arabia. Specific aim 2 will catalogue for each papillary thyroid carcinoma to include the full range of somatic mutations including single-nucleotide variants, insertions, deletions, copy number changes, translocations and other chromosomal rearrangements. Specific aim 3 will generate complementary catalogues of transcriptomic and epigenomic datasets from selected tumor cases that demonstrate abnormalities from aim 1 and 2.

The outcome of this study will provide a better understanding of PTC 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 PTC tumors.

PROGRESS: 50 paired samples of thyroid cancer haven been harvested and whole genomic sequencing has been completed in 10 samples.

COLLABORATIONS

National Collaborations:

- Department of Pathology and Laboratory Medicine, KFSH&RC
- Department of Oncology Centre, KFSH&RC
- Department of Surgery, KFSH&RC
- Department of Medicine, KFSH&RC
- Department of Pediatric Hematology/Oncology, KFNCCC, KFSH&RC
- Pathology Services Division, Saudi Aramco, Saudi Arabia

International Collaborations:

- Department of Pathology, University Medical Center Hamburg-Eppendorf,
- Hamburg, Germany.

ACCOMPLISHMENTS / ACHIVEMENTS

- Dr. Khawla S Al-Kuraya was selected to be member of editorial board of World Journal of Medical Genetics (WJMG) in January 6, 2011.
- Dr. Khawla S Al-Kuraya was selected to be senior member of editorial board of International Journal of Clinical and Experimental Pathology (IJCEP) March 2011.
- Dr. Khawla S Al-Kuraya was selected to be member of editorial board of Frontiers in Thyroid Endocrinology (Review Editorial Board) / March 2011.
- In 2011, a total of 15 full length manuscripts were published in reputable peer reviewed scientific journals.
- In 2011, we were able to submit 29 abstracts in different international scientific meetings.
- Significant findings from various studies that were performed during the year 2011 include the following:
  - FoxM1 was found to be over-expressed in 84.6% of DLBCL and was significantly associated with expression of ki67, MMP-2 and MMP-9

- FoxM1 was found to be expressed in 28.4% of PTC samples and was significantly associated with expression of XIAP, MMP-9 and Bcl-Xl.
- Thymoquinone treatment inhibits PI3-kinase/AKT and NFκB survival pathways in lymphoma cells leading to inhibition of cell viability and induction of apoptosis.
- P-Met was found to be activated in 69.9% of PTC and was significantly associated with expression of DR5.
- NFκB survival pathway has been shown to be pre-dominantly associated with activated B-cell (ABC) subtype of DLBCL.

FUTURE DIRECTION AND RESEARCH

Our long-term goal is to design better strategies to diagnose, prognosticate and improve the management of thyroid cancer in the Kingdom of Saudi Arabia. Human Cancer Genomic Research and Department of Genetics will perform large-scale genomic sequencing using the most current technologies. We continually adopt improvements in existing technology and invest in implementation of new sequencing technologies to enable whole genome sequencing of tumors for complete genomic analysis. As a part of ICGC project, we will do whole genomic sequencing using next generation sequencing technology mainly Illumina HighSeq2000. We will identify oncogenic driver mutations and find their relationship with thyroid cancer patho-biology including germline mutations and possible interacting environmental factors.

Complementing clinical research with basic scientific studies including in-vitro functional assays and in-vivo animal models will further enhance our research in the field of cancer. Determination of potential therapeutic targets will allow us to test newer pharmacological inhibitors with decreased toxicity as compared to conventional chemotherapy to improve the response to treatment. Within our research laboratory, we will continue using state-of-the-art approaches to study fundamental questions regarding cancers in Saudi Arabia and in the Middle East. In addition to basic research, there is also a strong emphasis on translating basic science advances into more effective and highly reliable diagnostic and therapies.

PUBLICATIONS

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INFECTION AND IMMUNITY

INFECTION AND IMMUNITY

CHAIRMAN
Mohammed N. Al-Ahdal

THE ESTABLISHMENT OF THIS DEPARTMENT WAS FINALIZED ON 29 December 2011. It is currently composed of 12 MSR staff members (Dr Mohammed Al-Ahdal, Dr Ahmed Al-Qahtani, Dr Sahal Al-Hajoj Alnakhli, Dr Mohamed Elfaki, Dr Alwaleed Alaidan, Dr Maha Al-Mozaini, Dr Damian Dela Cruz, Ms Suhair Abozaid [PhD Scholarship Recipent], Ms Marie Bohol, Mr Bright Varghees, Ms Mashael Al-Enazi and Mr George Bautista) and 3 Grant staff members (Ms Nisreen Khalaf, Ms Alria Datijan, and Ms Hanan Shaarawi). These are scientists, technologists, and other logostics staff. In addition, Professors Salvatore Rubino (Sassari University, Italy) and Atef Shibl (King Saud University, Riyadh) are Adjunct Principal Scientists. Collaborators include many physicians in KFSH&RC and local scientists (Dr Fatima Alhamlan, Dr Abiola Senok) , as well as international scientists (Uday Kishore [Brunel University, UK], Lionel Filion [Ottawa University, Canada])

At present, the Department of Infection and Immunity comprises four major sections, namely Immunocompromised Host (Dr Al-Mozaini, acting head), Microbial Pathogenesis (Dr Al-Ahdal, acting head), Molecular Virology (Dr Al-Qahtani, head), and Mycobacteriology (Dr Al-Hajoj Alnakhli, head). In addition, a Sterilization Room is made available for the Research Centre to use with an onsite attendant.

Currebt activities include molecular epidemiology of infectious agents and immunity to these microbes, as well as characterization of some oncogenic viruses. Investigations of new strains of microbes, obtaining grant funding, training, and tracing and identification of nosocomial pathogens are the major achievements. Future directions will cover microbial gene function studies, mechanisms associated with anitimicrobial resistance, immunological factors predisposing for infections, cellular immune response to infectious agents, and development and evaluation of vaccines.

RESEARCH PROJECTS

PROJECT TITLE: **Genoprevalence of human papillomavirus (HPV) in cervical specimens: a community study in Riyadh**

RAC # 2091 081

INVESTIGATORS: *Mohammed Al-Ahdal (PI), Ahmed Al-Qahtani, Kamal Elrady, Mohamed Shoukri, Damian dela Cruz, Suhair Abozaid, Marie Bohol. A master student from KSU (Walaa Al-Arnous) was put on this project*

PROJECT DESCRIPTION: It is well-documented that human papillomavirus (HPV) DNA and mRNA, particularly that of HPV-16 and HPV-18, were found in over 80% of cervical carcinoma tissues. There never has been any community study of HPV in Saudi Arabia. This study aimed to describe correlation between HPV positivity and cervical changes in this part of the world. We randomly obtained 519 cervical specimens with consent and demographic data from women attending clinics for routine check-up. The specimens were all subjected to Pap smear examination, HPV-DNA detection by PCR with general primers, and HPV genotype determination by reverse-line hybridization with HPV genotype-specific probes. One hundred and sixty four specimens (31.6%) were HPV-DNA positive by PCR, of these 30 showed cytological changes. Sixty four specimens were positive for cytological changes, of these 30 were also HPV-DNA positive. A strong correlation was found between HPV positivity and Pap smear test positivity [p <0.001, OR (95% C.I.) 2.833 (1.665–4.820)]. Our findings also indicated that hypertension [p=0.012] was also correlated with HPV infection. No other condition in the demographic data was correlated. There was significant association between each of these factors and HPV positivity. It was also found that the majority of positive HPV-DNA cases were among the women who were 25–44 years of age. These results could contribute to the management of HPV infections in Saudi Arabia and should assist health authorities to make proper decisions regarding bivalent or quadrivalent vaccination of women against HPV to reduce the infection and its associated cervical cancer disease.

PROJECT TITLE: **genome-wide association study of chronic hepatitis b virus infection reveals novel risk allele on 11q22.3**

RAC # 2060 040

INVESTIGATORS: *Ahmed Al-Qahtani, Hanif G Khalak, Fowzan S Alkuraya, Waleed Al-Hamoudy, Khalid Alswat, Faisal M Sanai, Ayman A Abdo*

PROJECT DESCRIPTION: Hepatitis B virus (HBV) affects millions of people worldwide. While some people are able to clear the virus following the first encounter, those who develop chronic infection manifest remarkable clinical heterogeneity that ranges from asymptomatic carrier state to cirrhosis and hepatocellular carcinoma (HCC). Despite extensive studies, little is known about genetic host factors that influence the outcome of chronic HBV infection. In this study, we conducted a genome-wide association study (GWAS) on a cohort of patients with chronic HBV infection. One particular SNP that is 16kb upstream of Ferredoxin 1 (FDX1) was found to have an association with complicated chronic HBV infection (cirrhosis and HCC) that reached GWAS significance, and was successfully validated on an independent set of samples. This first GWAS in an Arab population further demonstrates the utility of this approach in elucidating the genetic risk of HBV infection-related complications and highlights the advantage of conducting GWAS in different ethnicities to achieve that goal.

PROJECT TITLE: **Toll-like receptor 3 polymorphism and its association with 1 hepatitis B virus infection in Saudi Arabian patients**

RAC # 2060 040

INVESTIGATORS: *Ahmed Al-Qahtani, Mohammed Al-Ahdal, Ayman Abdo, Faisal Sanai, Mashael Al- Anazi, Nisreen Khalaf, Nisha A. Viswan, Hamad Al-Ashgar, Hind Al-Humaidan, Riham Al-Suwayeh, Zahid Hussain, Saud Alarifi, Majid Al-Okail, Fahad Al-Majhdi*

PROJECT DESCRIPTION: Hepatitis B virus (HBV) is the major causative agent of chronic liver complications including cirrhosis and hepatocellular

carcinoma (HCC). Individuals infected with HBV show a wide spectrum of disease manifestations ranging from asymptomatic carriers to HCC. TLR3 is part of the innate immune system that recognizes double-stranded RNA (dsRNA) and provides early immune response to exogenous antigen. The genetic polymorphisms such as single nucleotide polymorphisms (SNPs) in the TLR3 could be considered as factors for the susceptibility to viral pathogens including HBV. Due to lack of knowledge on the role of TLR3 polymorphisms in HBV infection, this study investigated the distribution of nine SNPs in the TLR3 gene and its association with Saudi Arabian patients infected with HBV. A total of 707 patients and 600 uninfected controls were examined for different parameters including the nine SNPs (rs5743311, rs5743312, rs1879026, rs5743313, rs5743314, rs5743315, rs111611328, rs78726532 and a newly identified SNP located at position 184322913 of chr4). The association analysis confirmed that only one SNP, rs1879026 (G/T), showed a significant difference (P=0.0480; OR=0.809, 95% CI=0.655–0.999) in the distribution between HBV carriers and uninfected controls. While, the rest of the SNPs showed no significant association with regards to HBV infection or in the progression to cirrhosis of the liver and HCC. Furthermore, haplotype analysis revealed that one haplotype GCGA (rs1879026 rs5743313, 62 rs5743314 and rs5743315, respectively), was associated significantly with HBV infection in this population. These findings indicate that genetic variations in the TLR3 gene could affect the outcome of HBV infection among Saudis.

PROJECT TITLE: **Single nucleotide polymorphisms 1 in CXCR1 gene and its association with hepatitis B infected patients in Saudi Arabia**

RAC # 2060 040

INVESTIGATORS: *Fahad Almajhdi, Mohammed Al-Ahdal, Ayman Abdo, Faisal Sanai, Mashael Al-Anazi, Nisreen Khalaf, Nisha A. Viswan, Hamad Al-Ashgar, Khalid Al-Kahtani, Hind Al-Humaidan, Riham Al-Swayeh, Zahid Hussain, Saud Alarifi, Majid Al-Okail, Ahmed Al-Qahtani*

PROJECT DESCRIPTION: This study aims to investigate whether the SNPs of CXCR1 gene, could predict the likelihood of viral persistence and/or disease progression. We investigated the association of two different SNPs (rs2234671, and rs142978743) in 598 normal healthy controls and 662 HBV patients from a Saudi ethnic population. The HBV patients were categorized into inactive carriers (n=428), active carriers (n=162), Cirrhosis (n=54) and Cirrhosis-HCC (n=18) sub-groups. Genetic variants in CXCR1 were determined by polymerase chain reaction (PCR)-based DNA direct sequencing. The frequency of the risk allele 'C' for the SNP, rs2234671 was found to be insignificant when the patient group was compared to the uninfected control group, however, a significant distribution of the allele 'C' of rs2234671 was observed among Active HBV carriers+cirrhosis+cirrhosis-HCC *vs.* Inactive HBV carriers with an OR=1.631 (95% C.I. 1.016–2.616) and p=0.032. However, no significant association was observed for rs142978743 when the distribution of risk allele was analyzed among the different patient groups (i.e. inactive carriers, active carriers, cirrhosis and HCC). Furthermore, the most common haplotype, Haplo-1 (AG), was found to have an insignificant frequency distribution between HBV cases and controls, while the same haplotype was found to be significantly distributed when active carriers+Cirrhosis+Cirrhosis-HCC patients were compared to inactive HBV carriers with a frequency of 0.938 and p=0.0315. Haplo-2 (AC) was also found to be significantly associated with a frequency of 0.058 and p=0.0163. The CXCR1 polymorphism, 68 rs2234671 was found to be associated with HBV infection and could predict the likelihood of viral persistence.

PROJECT TITLE: **Role of single nucleotide polymorphisms of KIF1B gene in HBV-associated viral hepatitis**

RAC # 2060 040

INVESTIGATORS: *Ahmed Al-Qahtani, Mashael Al-Anazi, Nisha A. Viswan, Nisreen Khalaf, Ayman Abdo, Faisal Sanai, Hamad Al-Ashgar, Mohammed Al-Ahdal*

PROJECT DESCRIPTION: Kinesin family member 1B (KIF1B) gene resides in the chromosomal region

1p36.22, which has been reported to have frequent deletions in a variety of human cancers. A recent GWAS study conducted on a Chinese population has reported the involvement of a KIF1B genetic variant in Hepatits B vius (HBV) related hepatocellular carcinoma (HCC). This study aims to investigate the significance of KIF1B genetic variants in HBV associated viral hepatitis in patients of Saudi Arabian ethnicity. TaqMan genotyping assay was used to investigate the association of three SNPs (rs17401966, rs12734551, and rs3748578) in 584 normal healthy controls and 660 HBV-infected patients. The patients were categorized into inactive carriers (Case I), active carriers (Case II), Cirrhosis (Case III) and Cirrhosis-HCC (Case IV) sub-groups. The genotypic distribution among patients and controls were comparable and therefore, no significant observations were recorded with regards to HBV infection. Similar insignificant observations were made when progression from HBV infection to HCC was analysed. Haplotype analysis was performed and the least frequent haplotype, ATA, was the only haplotype found to be significant, when HBVinfected patients were compared to healthy controls with a p value of 0.038. A similar analysis was performed among the different sub-groups in order to determine whether these SNPs were associated with the advancement of the disease. However, no significant differences were observed in any of the comparisons. The three KIF1B polymorphisms investigated in this study showed no significant association with HBV infection or with HBV-associated HCC.

PROJECT TITLE: **Cytokine responses in patients with pulmonary and extra-pulmonary tuberculosis**

RAC # 2030 001/KACST # AT-26–41

INVESTIGATORS: *Mohamed G. Elfaki and, Abdullah A. Al-Hokail*

PROJECT DESCRIPTION: Human tuberculosis (T.B.), one of the most widespread infectious disease, is the leading cause of death due to a single infectious agent among adults in the world. The disease is commonly caused by *Mycobacterium tuberculosis*, which infects primarily cells of the mononuclear phagocytic system with consequent cellular perturbation and debilitation of the host. Since cytokines are mediators of cell-to-cell interactions, elucidation of their regulatory role is important in understanding the pathophysiology of T.B. In this study, we proposed a two-fold approach to investigate the regulatory role of cytokines in patients with tuberculosis. In the first approach, cytokines level in plasma samples of patients with pulmonary and extra-pulmonary T.B. will be studied by ELISA. In the second approach, the patterns of cytokine gene expression and protein level will be studied *in vitro* by using mononuclear cells as target cells. The threshold detection of cytokines in both systems would provide insights into possible means of immune intervention as well as in the prediction of T.B. status. Thus, the compendium knowledge of cytokines profile would enhance our judgment about the progNOSis of T.B. and pave the way towards future use of cytokines as adjuvant in the treatment regimen of tuberculosis. Additionally, anticipated differences in cytokine responses between pulmonary and extra-pulmonary T.B. might be of diagnostic value at certain stages of disease progression.

The project final progress report has been submitted and accepted by both reviewer' and KACST scientific committee. In this report, our data showed that there was an overexpression of chemokines and growth factors coupled with underexpression of cytokines of adaptive immunity (IFN-γ, IL-12, and TNF-α) and the counter- regulator cytokine, IL-10 in an untreated patients with active pulmonary TB. The overexpressed chemokines include MCP-1, MIP-1, GRO-α, ENA-78, leptins, and angiogenins while the overexpressed growth factors include TGF-β, EGF, VEGF, and PDGF-BB. However, stimulation of tuberculous peripheral blood mononuclear cells (PBMC) with antigens derived from *Mycobacterium tuberculosis* (MTB) showed an enhanced secretion of IFN-γ and increased production of TNF-α and IL-10 with complex MTB antigens. Quantification of the overexpressed growth factors showed abundant secretion of TGF-β, VEGF, and EGF in plasma of tuberculous patients compared to normal control subjects. The protein expression of the model growth factors (TGF-β and VEGF) coincided well with their gene expression using RT-PCR. However, after 3 months of antituberculosis therapy, the level of tested growth

factors was significantly reduced and correlated well with clinical improvement. The molecular basis of effective therapy and improved immunity in tuberculous patients was further supported by delineating the expression of iNOS and no production, a known mediator that halt the multiplication of MTB. Our data showed an enhanced expression of iNOS molecule in RNA isolated from tuberculous PBMC-stimulated with MTB-culture filtrate protein (CFP). The enhanced expression of iNOS coincided with increased production of no in tuberculous PBMC culture. Taken together, these results suggest that the enhanced production and expression of growth factors in tuberculous patients might be implicated in the host response to MTB infection in damaged organs. The increased production of no coupled with the overexpression of iNOS in PBMC-stimulated with CFP suggest that this antigen is important in MTB immunity. Further, the plasma level of growth factors expression before and after therapy may be used as a powerful marker for treatment efficacy and/or failure.

PROJECT TITLE: **Surveillances, studying epidemiology of drug resistant tuberculosis and their impact on National Tuberculosis Program**

RAC # 2080 038/KACST#: AT-26–110

INVESTIGATORS: *Sahal Al-hajoj, Fahad Al-rabiah, Zeyad Memish, Naelah Abou Aljadaeel and Sahar Al-Thawadi*

PROJECT DESCRIPTION: In this project we attempted to evaluate the Mycobacterium tuberculosis drug resistant rate in the country as a whole. Isolates were collected from all TB cultures laboratories for one year. As results more than 3000 isolates were collected. Drug susceptibility testing was carried out for 1904 isolates. Our data showed that the rate of MDR-TB drug resistance is 4%. Mono drug resistance data showed variation in the rate. Final report was submitted to KACST.

PROJECT TITLE: **Detection of IFNγ production for diagnosis latent tuberculosis in patients for kidney transplant**

RAC # 2070 013

INVESTIGATORS: *Sahal Al-hajoj and Abdulrhman Alrajhi, Fahad Al-Rabiah, Ashraf Attia, Hazem Al-Gamal and Ihab Mohmoud*

PROJECT DESCRIPTION: This project is targeting to evaluate QuantiFERON TB gold test as new diagnostic tool to detect dormant TB in very vulnerable group (kidney transplant patients. To this moment 237 patients were recruited and their bloods were tested. The ultimate aim is to evaluate the accuracy of the test in comparison to PPD test.

PROJECT TITLE: **Evaluation of QuantiFERON-TB gold in patients with extrapulmonary tuberculosis**

RAC # 2090 016

INVESTIGATORS: *Sahal Al-hajoj and Abdulrhman Alrajhi, Ali Al-Barrak, Mishirah Enani*

PROJECT DESCRIPTION: Usually diagNOSis of extra-pulmonary TB is difficult and sometimes required biopsy. In this project once again we are evaluating the efficiency of the QuantiFERON-TB gold test to detect extrapulmonry infection.

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 # 2091 046

INVESTIGATORS: *Sahal Al-hajoj and Abdulrhman Alrajhi, Abdullah Al Khenizan, Abdulaziz Al Saif, Ali Alzahrani, Sahar Al-Thawadi and Haifa Al- Talhi*

PROJECT DESCRIPTION: Health care workers are among high risk groups whom might get the TB infection. The traditional diagnostic method which is used to detect infection (dormant) among health care worker is PPD test. However, we believe QuantiFERON-TB gold test is more efficient than PPD test to detect dormant TB. As result this project was designed to evaluate the QuantiFERON-TB gold test as a new diagnostic tool. Eventually data generated from this project will be compared to PPD test.

MOLECULAR BIOMEDICINE PROGRAM

MOLECULAR BIOMEDICINE PROGRAM

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BIOINCUBATOR PROGRAM
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FUNCTIONAL SECTIONS
Bioinformatics
Interferons and Cytokines (*Mechanisms of Disease*)
Molecular Biotechnology
Molecular Therapeutics

THE OBJECTIVE OF THE MOLECULAR BIOMEDICINE PROGRAM IS TO investigate mechanisms of diseases and develop necessary tools with potential translational outcome in therapy or in medical biotechnology. The program currently focuses on a medically important family of genes associated with regulating mRNA stability and translation which are perturbed as a result of disease. The program has a unique and internationally known research platform which is applicable to several chronic disease conditions that impact the health care in Saudi Arabia including inflammatory, infectious, and cardiovascular diseases, and cancer.

SELECTED ACHIEVEMENTS FOR 2011

- Development of IFN-responsive biosensor expression cassettes and cell lines We have constructed and evaluated more than 100 reporters reflecting IFN and virus response element heterogeneity. According to Reviewers, this is the largest promoter enhancer study in a single study.
- An International Patent Application -International Patent Application. April 2011: "Multiple Interferon and Virus Response Element Cell-Based Fluorescence System"
- Granted Patent: No. 2005819306. Hybrid 3' Untranslated Regions Suitable for Efficient Protein Expression in Mammalian Cells. European Patent.
- Plenary Session Speaker. Khalid S. A. Khabar. Symposium on IFN-stimulated Genes. Prato, Italy RNase L has an essential role in the p21 mediated growth arrest.
- Editorial Board, Member. Khalid S. A. Khabar, Journal of Interferon and Cytokine Research. Official Journal of the International Society for Interferon and Cytokine Research.

RAC-APPROVED RESEARCH PROJECTS

- Regulation of the Expression of Chemokines During Cell Differentiation and Consequences in Chronic Inflammation.
- Molecular regulation and functional properties of novel IFN-stimulated gene, NT5C3.
- The miR29a-TTP axis regulation of the RNA binding protein, HuR, and CXCR-4 in invasive breast cancer.
- Reagent Production Project (KACST Bio Incubator Program).
- Cloning Free and Enhanced Reporter Gene Technology (KACST Bio Incubator Program)

FUTURE RESEARCH DIRECTION

The program still shares the same focus and direction in the future. A large-scale view and analysis of RNA-stability changes during disease will be facilitated by various tools that have been developed in the past few years. The mechanistic studies of the diseased pathways in cancer will be carried out in order to device therapeutic approaches to normalize the aberrant mRNA stability.

RECENT PUBLICATIONS

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- Al-Khalaf HH, Colak D, Al-Saif M, Al-Bakheet A, Hendrayani SF, Al-Yousef N, Kaya N, Khabar KS, Aboussekhra A. p16(INK4a) positively regulates cyclin D1 and E2F1 through negative control of AUF1. *PLoS One*. 2011;6(7):e21111.
- Halees AS, Hitti E, Al-Saif M, Mahmoud L, Vlasova-St Louis IA, Beisang DJ, Bohjanen PR, Khabar K. Global assessment of GU-rich regulatory content and function in the human transcriptome. *RNA Biol*. 2011 Jul 1;8(4):681–91.
- Al-Souhibani N, Al-Ahmadi W, Hesketh JE, Blackshear PJ, Khabar KS. The RNA-binding zinc-finger protein tristetraprolin regulates AU-rich mRNAs involved in breast cancer-related processes. *Oncogene*. 2010 Jul 22;29(29):4205–15.
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- Hitti E, Al-Yahya S, Al-Saif M, Mohideen P, Mahmoud L, Polyak SJ, Khabar KS. A versatile ribosomal protein promoter-based reporter system for selective assessment of RNA stability and post-transcriptional control. *RNA*. 2010 Jun;16(6):1245–55.
- Al-Ahmadi W, Al-Ghamdi M, Al-Haj L, Al-Saif M, Khabar KS. Alternative polyadenylation variants of the RNA binding protein, HuR: abundance, role of AU-rich elements and auto-Regulation. *Nucleic Acids Res*. 2009 Jun;37(11):3612–24.
- Nguyen Chi M, Chalmel F, Agius E, Vanzo N, Khabar KS, Jégou B, Morello D. Temporally regulated traffic of HuR and its associated ARE-containing mRNAs from the chromatoid body to

polysomes during mouse spermatogenesis. *PLoS One*. 2009;4(3):e4900.

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- Al-Haj L, Al-Ahmadi W, Al-Saif M, Demirkaya O, Khabar KS. Cloning-free regulated monitoring of reporter and gene expression. *BMC Mol Biol*. 2009 Mar 8;10:20.
- Al-Ahmadi W, Al-Haj L, Al-Mohanna FA, Silverman RH, Khabar KS. RNase L down modulation of the RNA-binding protein, HuR, and cellular growth. *Oncogene*. 2009 Apr 16;28(15):1782–91.

STEM CELL &
TISSUE RE-ENGINEERING
PROGRAM

STEM CELL & TISSUE RE-ENGINEERING PROGRAM

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THE "STEM CELL THERAPY PROGRAM" FOCUSES ON INVESTIGATING the molecular and cellular mechanisms of stem cell biology and their application for therapeutic use in a number of clinical areas including spinal cord injuries, cardiovascular, neurodegenerative, renal, liver and autoimmune diseases, diabetes and cancer. The department is working towards achieving the goal of excellence in stem cell research and therapy 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 the Imperial College London and members of the Harvard Medical School and its affiliated Hospitals, in particular, The Transplantation Center, and The Renal Divisions at The Brigham and Women's Hospital and Children's Hospital Boston, and The Massachusetts General Hospital, The Dana-Farber Cancer Institute, and The Massachusetts Institute of Technology (MIT), United States of America. We are convinced that a well-funded team of scientists with expertise in tissue engineering, stem cell biology and transplantation will bring the dream of curing human disease by implanting fabricated organs to reality. We are moving the field forward tremendously and this have led to our conviction that the generation of living constructs for human therapy, including whole organs such as a heart, liver, pancreas, lung and kidney, is close at hand and will happen at the KFSH&RC. KFSH&RC is recruiting now the best Saudi biologists, engineers, and clinicians in the world and we firmly believe that a coordinated Program that brings all these talents together will achieve our ultimate goal - the fabrication of vital organs through bioengineering. Achieving this goal will change medicine as we know it. Importantly, the program is committed to training, recruiting and advancement of Saudi scientists, technicians and students.

LIST OF SIGNIFICANT AND SCIENTIFIC ACHIEVEMENTS

- Thirty (30) on-going RAC approved research projects.
- Three (3) Projects were approved for funding by KACST and the National Plan for Science and Technology. Other projects are initially accepted.
- Eight (8) full scientific publications of research work published in prestigious journals.
- Five (5) full scientific publications of research work submitted in prestigious journals.
- Ten (10) manuscripts in preparation.
- Eleven (11) Abstracts presented in international conferences/meetings.
- Eleven (11) Abstracts presented in national scientific conferences/meetings.
- International Patent Applications on major scientific discoveries for diagnostics and patient care have been issued to King Faisal Specialist Hospital and Research Centre, Riyadh, KSA.
- Five (5) Memoranda of Understanding (MOU) were signed with prestigious international institutions.
- Recipient of Award of the Best Presentation and Outstanding Achievement in the 16th World Congress on Advances in Oncology and The 14th International Symposium on Molecular Medicine, October 06–08, 2011, Hotel Rodos Palace, Rhodes Island, Greece, awarded to Dr. Ayodele Alaiya.
- The Saudi Kidney Health Program was launched and affected families have been successfully recruited into the study.
- Transformed and equipped the Proteomics and Flow Cytometry Units making them into functional laboratories of International Standards.
- Supported young Saudi Arabian researchers, in pursuing training/higher education and post-doctoral fellowships at respected international institutes: Harvard Medical School, Harvard Hospitals, Massachusetts College of Pharmacy & Health Sciences (MCPHS), Boston, MA USA, Imperial College London, Canadian Universities, University College London, University of South Paris, University of Portsmouth, Toronto Institute Canada, Aberdeen University, UK, and University of Nottingham, UK.
- Established successful collaboration with national and international institutions on both research projects and education programs such as; The Harvard Fellowships (4 Awards) & 1 Pharm D at Massachusetts College of Pharmacy & Health Sciences (MCPHS), Boston, MA USA, 5 PhD Students in UK, In-House Training (Saudi Students and Employees). Regular training of technical staff abroad, attending professional meetings to present research work at international and national scientific meetings/conferences.
- Host "Summer Training Program" for gifted and future scientist students.
- Established the foundation of The Saudi HLA Genome Database to advance the fields of hematopoietic stem cell transplantation and kidney transplantation in the Kingdom of Saudi Arabia.
- Potential Identification of new HLA alleles specific for the Saudi population, pending verification.
- Identification of HLA Alleles in Normal Saudi Individuals by Sequence Based Typing.
- Correlation of Saudi population associated HLA genes and certain autoimmune diseases progression and transplant outcome.
- Generating powerful DC which may lead to national immune therapeutic modulate for CML patients based on Saudi genome.
- A "Silver Award", for Excellent Research from King Abdul-Aziz City for Science and Technology (KACST) was received by Dr. Khalid Hussein, Senior Scientist at Stem Cell Therapy Program.

SIGNED MEMORANDA OF UNDERSTANDING

1. KFSH&RC and INSERM and University Hospital Center (France), 4th of November 2007.
2. KFSH&RC and The Harvard Medical School (USA), 19th of January 2008.
3. KFSH&RC and The Transplantation Research Centre at Harvard, January 2008.
4. KFSH&RC- PSCDR- Swiss Stem Cell Bank, Founders Council Ceremony, Jeddah, Saudi Arabia, 09 September 2008.
5. KFSH&RC and Karolinska University Hospital and Lund University, Sweden (Established collaborative project since 2009).

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.
- Karolinska Hospital and Institute, Stockholm, Sweden.
- Lund University, Lund, Sweden.
- Dubai Harvard Foundation for Medical Research, Dubai, UAE.
- Imperial College, United Kingdom.
- 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.

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).
- DNA Cell Cycle Repair.

PATENTS ISSUED

INVENTOR: Chaker N. Adra. Lysosomal-associated multispanning membrane protein, LAPTM5 and nucleic acid encoding LAPTM5. 6,153,403. 2000 Nov 28.

INVENTOR: Chaker N. Adra. HT.sub.m4 methods of treatment and assays, agonists and antagonists. 5,972,688. 1999 Oct 26.

INVENTOR: Chaker N. Adra. D4 gene and methods of use thereof. 5,767,073. 1998 Jun 16.

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INVENTOR: Chaker N. Adra. Method for detecting a predisposition to asthma and atopy. US2003165992. 2003 Sep 4.

INVENTOR: Chaker N. Adra. Methods and Compositions for Cell Cycle Regulation. Application Number US11779381. Publication date 06/26/2008 U.S.

INVENTOR: Chaker N. Adra. HTm4 Used For Cell Cycle Regulation through Its Interaction with Kap Application Number US2006001844. Publication date 07/19/2007.

INVENTOR: Chaker N. Adra. Granulocyte Subtype Selective Receptors and Ion Channels and Uses Thereof. Application Number US5007519. Publication date 10/13/2005.

RAC APPROVED RESEARCH ACTIVITIES

PROJECT TITLE: **Development of Autologous Stem Cell Therapy for Patients with Severe Peripheral Arterial Disease of the Lower Limbs-A Phase II Non-Randomized Study**

RAC # 2081 021

INVESTIGATORS: *Dr. Chaker Adra (PI), Dr. Nahar Al-Anezi Dr. Hind Al-Humaidan,(Co-PI), Dr. Ayodele Alaiya, Dr. Fouad Hassan Al-Dayel, Dr. Tauqir Ahmed Rana, Dr. Morad Al-Kaff, Dr. Tarek Al-Owaidah, Dr. Bassel Safi*

ADVISORS: *Dr. Mohamed H. Sayegh, Dr. Michael S. Conte*

PROJECT DESCRIPTION: The primary aim of this study is to use autologous transplantation of mononuclear stem cells (MNCs) derived from either bone marrow (BM) or peripheral blood from patients with severe Critical Limb Ischemia (CLI) and to assess the efficacy, safety and feasibility of treatment protocol. The study in addition; aims to identify Peripheral Arterial Disease (PAD)–associated biomarkers using global protein expression analysis.

METHODS: Twenty patients diagnosed with CLI; that are not amenable to any intervention or bypass-able patients with high risk for surgery will be recruited for the study. MNCs will be sorted in the lab either from harvested iliac crest BM or from peripheral blood. MNCs will then be injected either intramuscular alone in the calf of the ischemic leg or in combination with intra-arterial injection via the femoral artery of the ischemic leg. Patients will be assessed for 3 to 12 months post transplantation to the outcome of the treatment.

We will also use proteomics approaches to identify potential biomarkers from tissue biopsies and blood samples that could be useful in the development of Stem Cells for therapeutic strategies in regenerative disorders and arterial occlusive diseases.

SIGNIFICANCE: The outcome of this clinical trial will improve our understanding of the potential use of Stem Cell therapy as an alternative intervention for patients with severe PAD. In addition, association between results from bench-work with results obtained in the clinical trial will further assist the identification of cellular and molecular PAD-associated biomarkers, towards improving diagnosis of PAD and developing better treatment strategies.

PROGRESS/MAJOR FINDINGS

1. The first progress report was submitted
2. Only two patients have been recruited and injected with stem cells, but the patients were lost to follow up.
3. We are making efforts to involve other satellite hospitals within and outside Riyadh to refer patients who meet the study inclusion criteria. It is anticipated that number of patient recruitment will be improved to allow meaningful evaluation of treatment protocol.

PROJECT TITLE: **Expansion and Differentiation of Human Embryonic and Hematopoietic Stem Cells Using Proteomics: The Therapeutic Use of Stem Cells in Disability Research**

RAC # 2080 050 (ARP 29–95)

INVESTIGATORS: *Dr. Chaker Adra (PI), Dr. Hind Al-Humaidan, Dr. Ayodele Alaiya, Dr. Andrew Wetzig, Dr. Maha Al-Mozaini, Dr. Saleh Al-Othman, Mr. Pulicat S. Manogaran, Dr. Hazem Ghebeh*

PROJECT DESCRIPTION: A primary goal of this work is to find new ways to identify stem cells and discover what sort of media they need for growth *in vitro* and how to differentiate them reproducibly into variable specific cell lineages. We will look at how different molecules changes using high-throughput proteomics to map the cellular protein profile and

the secreted proteins in the culture media to develop standardized protocols for reproducible tissue engineering. We are also going to label these proteins with fluorescent dyes and compare the protein profile of the starting material with the cultured cells (this is called differential two dimensional gel electrophoresis, DIGE) and use this to follow changes in stem cells as they grow and differentiate and give an intelligent feed-back system of how protein regulation is changing as the culturing conditions are varied.

This is a collaborative research project between the Proteomics Facility of the Stem Cell Therapy Program at KFSH&RC, Riyadh, Saudi Arabia and the Proteomics Facility at Imperial College, London with a major aim to help the growing number of individuals suffering from disability in Saudi Arabia. Integration of proteomic studies carried out at the two complementary proteomics centers will serve the purpose of stem cell characterization for clinical applications.

PROGRESS: Our preliminary 2-DE DIGE separation of umbilical cord stem cells was done with satisfactory resolution. We plan to carry out the same type of analysis using discarded samples from the IVF clinic.

PROJECT TITLE: **Investigating the Immunogenicity of Breast Cancer Stem Cells**

RAC # 2080 045 (Funded: ARP 24–29)

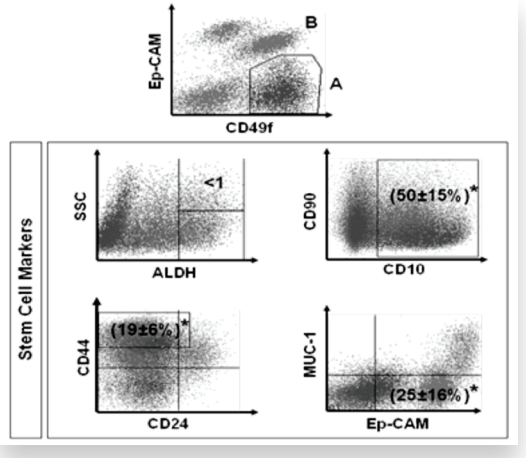
INVESTIGATORS: *Dr. Chaker Adra (PI), Dr. Hazem Ghebeh, (Co-PI), Dr. Monther Al-Alwan, Dr. Taher Al-Tweigeri, Dr. Khalid Al-Faqeeh, Ghida Sleiman*

PROJECT DESCRIPTION: There is accumulating evidence that cancer is originated and sustained by cells called "cancer stem cells (CSC)". These cells share many characteristics of the normal stem cells including the self-renewing ability. Thus, it is possible that they also have the immune privilege properties of normal stem cells.

This proposal studies the phenotype of normal and cancer stem cells and how cancer stem cells effect antigen presentation and immune response generation. It also investigates the role of CSC in the creation of immune suppressive microenvironment, which finally leads to tumor escape from the immune system surveillance.

The first step was to identifying the population of breast cells that contains the stem cells. Up to date, there are conflicting results in the literature on the phenotype of normal breast stem cells. They are described as Ep-CAMhigh, CD49f+, Ep-CAM low CD49f+ cells, CD44high/CD24low or ALDH+ cells.

Single cells that express the stem cell markers Ep-CAM+, CD10+, CD44high/CD24low or ALL (cell that express all stem cell markers) were sorted with Fluorescence Assisted Cell Sorting (FACS) followed by mammospheres formation.



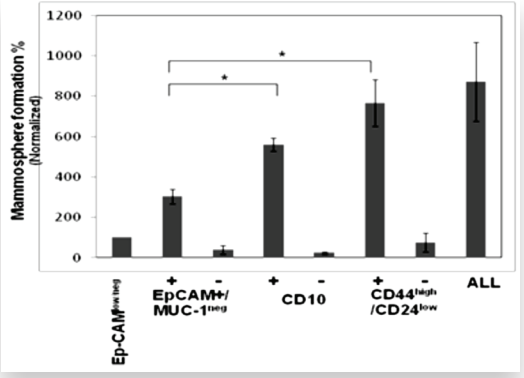


Figure 1. Ep-CAMlow /CD49f+ (A) expressed three stem cell markers which among them CD44high/CD24low had the highest mammospheres formation ability.

Results show that cells with CD44high/CD24 had the highest mammospheres formation ability as compared to Ep-CAMlow main cell population.

PROJECT TITLE: **Genetic Basis of Kidney Disease in the Kingdom of Saudi Arabia**

RAC # 2080 042

INVESTIGATORS: *Dr. Chaker Adra (PI), Dr. Martin Pollak (PI), Dr. Khaldoun Al-Romaih, Dr. Hamad Al-Mojalli, Dr. Hadeel Al-Manea, Dr. Ayodele Alaiya, Dr. Hind Al-Humaidan, Dr. Mamdouh Al-Baqumi, Noura Atallah, Alia Iqniebi*

PROJECT DESCRIPTION: The focus of this collaborative research is on kidney nephropathies, with a particular interest in the study of the genetics, and epigenetics of renal diseases and the potential application of stem cells for novel therapies. In the first project in this collaborative effort we are recruiting families with kidney disease to determine if defects in known genes can account for the disease by analysis of DNA sequence and to explore the possibility of identifying novel disease causing mutations/genes. In families in which multiple members share the same kidney disease, we are using genetic linkage analysis to identify chromosomal regions that are associated with the disease inheritance. We will then identify the specific DNA change within these regions. In addition expression proteomics will be conducted towards discovery biomarkers for accurate typing and classification of kidney diseases.

PROGRESS:

1. *IDENTIFICATION AND RECRUITMENT OF SUBJECTS WITH FSGS:* In the past 10 months we ascertained FSGS families and sporadic FSGS patients. We extended each family maximally. This required characterizing not only individuals with FSGS, but also analyzing the phenotype of other family members by assessing urine protein excretion, serum creatinine, and standard urinalysis. We ascertained families based on the criteria listed in the methods of the original proposal, in brief, at least one family member have biopsy documented FSGS which appeared to be primary rather than secondary, and other family members are considered to be affected if they have urine micro albumin/ creatinine ratio of greater than or equal to 300 mg/g creatinine on repeated measurements, indeterminate if urine microalbumin is between 30 and 300 mg/g creatinine and unaffected if < 30 mg/g. We obtained blood samples from consented participants and DNA extraction was performed on all samples. Urine also was obtained for protein measurement in family members with no signs of the disease to confirm their phenotype. We will continue to actively ascertain more families through an established network of nephrologists and renal pathologists throughout Saudi Arabia.

2. *MUTATIONAL ANALYSIS OF KNOWN FSGS GENES IN THE SAMPLE SET:* The number of disease causing mutations identified in the ACTN4, TRPC6, and CD2AP genes is relatively small. Identifying additional mutations that cause human disease is important both for understanding the genetic basis of FSGS as well as for understanding structure-function relationships within the encoded proteins. We performed mutational screen of a number of known FSGS genes including ACTN4, NPHS2, and TRPC6 in patients with FSGS and we Continue determination of FSGS-associated variants in

these known genes as this is essential both for understanding the biology of this disease as well as structure/function and genotype/phenotype relationships. We will resequence FSGS genes in probands from new FSGS families and subjects with sporadic FSGS as they are recruited into these studies by our collaborating physicians.

3. *GENETIC LINKAGE ANALYSIS TO IDENTIFY NEW DISEASE LOCI:* In our recent article in the American Journal of Kidney Diseases (AJKD), we coupled genotyping and high-throughput sequencing technologies to accurately track genetic traits (Al-Romaih et al, AJKD 2011). Using these technologies to make precise genetic diagnoses helped us to distinguish between disease entities with mixed phenotypic and histopathologic patterns, to draw conclusions from analyses performed on a small number of individuals, and to realize the significance of possible NPHP1/MALL locus contribution to kidney disease in KSA. Our 2011 report was the first to successfully use alternative technology based on homozygosity mapping coupled with whole-exome sequencing to overcome the diagnostic complexity of focal segmental glomerulosclerosis (FSGS). In follow-up to our previous findings and in line with our aim to identify new disease loci harboring disease causing genes we continued our genetic analysis of subjects recruited to this study and made the following progres;

GENETIC LINKAGE IN CONSANGUINEOUS FAMILIES FROM SA: In our continuous effort to find new FSGS-causing genes in consanguineous families from KSA, we genotyped extended families with history of proteinuria and FSGS-like histopathologic findings. These families were recruited in Year-One of the study period. The approach we used was similar to that reported in our article in AJKD. In brief, Using Sanger dideoxynucleotide DNA sequencing, we resequenced PCR-amplified segments containing coding sequences and flanking splice sites of 4 known FSGS/nephrotic syndrome genes (NPHS2, ACTN4, TRPC6, and INF2) in members of these families. Mutational analysis detected no mutations in the sequenced FSGS/nephrotic syndrome genes. We then performed genome-wide genotyping of SNPs using a commercial microarray designed to probe 250,000 sites. DNA samples from 10 informative members of two independent families were so far genotyped (FAM002 and FAM012, see figure below). SNP genotyping data were analyzed using a similar approach to that published by us in AJKD to identify homozygous regions shared in affected individuals. Shared homozygous regions were detected in affected subjects of FAM002 including regions on chromosomes 1, 12, 15, 19 in addition to sharing homozygous runs on chromosome X when the grandfather was included in the analysis. Affected siblings in FAM012 shared homozygous regions on chromosomes 2, 3, 4, 5, 7 and 15. We believe combining the findings of this analysis with the findings of our ongoing whole-exome sequencing of affected subjects from these two families will enable us to identify disease causing genes responsible for kidney disease in these two families.

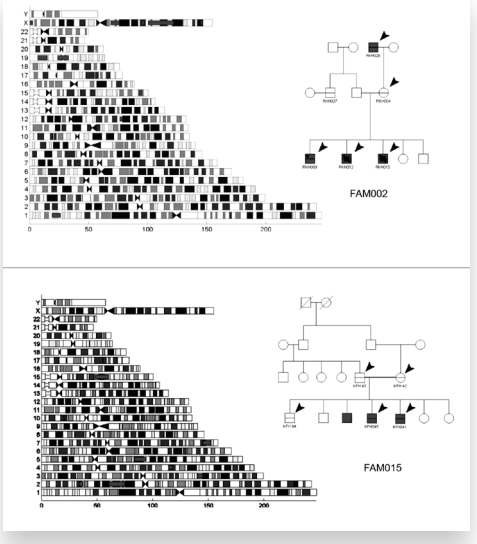


Figure 2: Family pedigrees and SNP genotyping results. Arrowheads point to genotyped members. Red boxes are affected members. Blue boxes are affected who had kidney transplant. Red rectangles on chromosome image indicate shared homozygous regions in affected members.
Square = male and circle = female.

FOLLOW UP ON NPHP1/MALL ALLELE FREQUENCY IN SAUDI ARABIAN POPULATION: Our 2011 report highlighted the significance of NPHP1/MALL deletion in patients presented with FSGS-like diagnosis. The deletion was detected between SNP rs7575835 and SNP rs7575835 consistent with possible homozygous deletion of this genomic region. A previous independent haplotype analyses in NPHP1 families strongly suggested that the deletions detected in those families were not due to a founder effect (Konrad et al, HMG 1996). However, findings in our genotyping experiment indicated that the deletion in the KSA families was an event that occurred in a common ancestor and that the deletion and surrounding chromosomal region was passed through many generations to the affected individuals. In our study the SNP array contained 36 SNPs from within the homozygous run of 2 Mb (between rs6754115 at genomic position 109,328,776 and rs17464100 at genomic position 111,284,252 of NCBI 36), which were found to be homozygous in affected members. This suggested the possibility that this deletion may have a nontrivial frequency in the Saudi Arabian regions from which these families originate. To investigate the frequency of NPHP1/MALL allele in Saudi Arabian population, I utilized a quantitative PCR based assay to analyze kidney patient samples and healthy controls that were recruited to this study in Year-One of the project duration (please see 2009 report). Preliminary findings suggest that there is no NPHP1/MALL deletion in the analyzed 15 affected subjects and 15 healthy controls. These results are limited by such a small sample number and prompt the importance of expanding this study to cover a large number of kidney disease patients and healthy controls in Saudi Arabia.

4. *RENAL PROTEOMICS ANALYSIS:* Proteomic Analysis of FSGS and Lupus Nephritis has been conducted and a number of proteins were differentially expressed and will be validated as renal biomarkers: A manuscript on Lupus Nephritis class IV Global Versus Segmental has recently been submitted to the Journal of the American Society of Nephrology, April 2011).

PROJECT TITLE: **Investigating the Role of Cellular Inhibitory Proteins in Eosinophils Apoptosis: Implication in Asthma/Atopy**

RAC # 2080 026

INVESTIGATORS: *Dr. Bandar Al-Saud (PI) Dr. Chaker Adra (PI), Dr. Ayodele Alaiya, Dr. Monther Al-Alwan, Dr. Hind Al-Humaidan, Dr. Ameera 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: **Identification and Therapeutic Targeting of ABCB5+ Tumor Stem Cells**

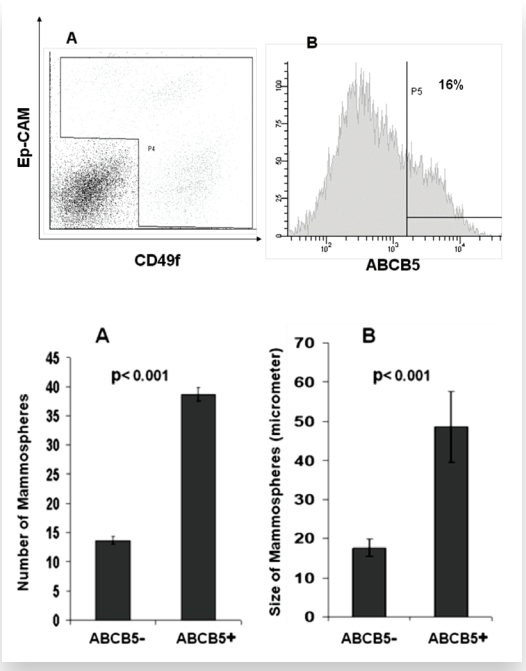
RAC # 2080 023 (Funded: MED 483–20)

INVESTIGATORS: *Dr. Chaker Adra (PI), Dr. Dahish Ajarim, Dr. Hind Al-Humaidan, Dr. Fouad Hassan Al-Dayel, Dr. Ayodele Alaiya, Dr. Asma Tulbah, Dr. Tarek Amin, Dr. Imaduddin Kanaan, Dr. Hazem Ghebeh, Dr. Khaled Al-Faqeeh*

PROJECT DESCRIPTION: ATP binding Cassette B5 (ABCB5) is an energy-dependent drug efflux pump for the fluorescent probe rhodamine and to drugs like doxorubicin. This transporter is abundantly expressed by normal melanocytes, and it has been

found to identify the small population of cancer stem cells in melanoma. Very little is known about the expression of this molecule in normal and malignant breast.

Cells that express ABCB5 were sorted using FACS and allowed to form mammospheres (Figure 3A). ABCB5+ cells formed more mammospheres than ABCB5neg counterparts (Figure 3B) supporting their higher expression in breast stem/progenitor cells.



PROJECT TITLE: **Proteomic Analysis of Human Breast Cancer Stem/Progenitor Cells**

RAC # 2080 021, (Proteomics)

INVESTIGATORS: *Dr. Ayodele Alaiya (PI), Dr. Chaker Adra (PI), Dr. Fouad Al-Dayel, Dr. Hind Al-Humaidan, Dr. Dilek Colak, Dr. Ghebeh Hazem, Dr. Asma Tulba, Dr. Taher Al-Tweigeri, Prof. Godovac-Zimmermann J.*

PROJECT DESCRIPTION: The goal of this study is to investigate the critical molecular alterations affecting breast cancer stem cells, and how they interact with their microenvironment. The phenotypic characteristics of mammary stem cells will be defined at the protein level using a proteomics approach. This will provide information which could be used to improve both the diagnosis of breast cancers and the ability to predict clinical outcomes and response to the current treatment modalities. Furthermore, new selective therapeutic strategies could be developed targeting breast cancer stem cells while sparing normal stem cells.

PROGRESS, MAJOR FINDINGS:

1. Established efficient logistics for sample collection
2. Selection of a group of markers known to enrich for stem/progenitor cell populations
3. Optimized cell culturing conditions for the isolation of stem/progenitor cells
4. The resulting mammospheres were stored frozen at -80°C pending proteome analysis
5. Developed protocols for protein extraction methods from small numbers of sorted stem cells (2-DE/LC/MS/MSAn abstract and poster presentations at The 2nd Conference on Stem Cell and Regenerative Medicine, 13–16 November 2011 (17–20 Dhu Al Hijjah 1432, College of Medicine, King Saud University, Riyadh, Saudi Arabia
6. An abstract and poster presentations accepted at 10th Annual meeting of the International Society for Stem Cell Research, June 13- 16, 2012, Yokohama, Japan (*http://www.isscr.org/Annual_Meeting_Home.htm*).

PROJECT TITLE: **The Propagation of Mesenchymal and Neural Stem Cells from Adult Olfactory Mucosa**

RAC # 2080 007

INVESTIGATORS: *Dr. Chaker Adra (PI), Dr. Ayodele Alaiya, Dr. Andrew Wetzig, Dr. Hind Al-Humaidan, Dr. Imaduddin Kanaan, Dr. Monther Al-Alwan*

PROJECT DESCRIPTION: The overall aim of this project is to develop a therapeutic adult stem cell treatment for spinal cord injuries. Both mesenchymal and neural stem cells could be harvested from the patient's olfactory mucosa and used together to treat the injured spine. In this way the immunosuppressive and neurotrophic properties of mesenchymal stem cells (MSCs) would be combined with the ability of neural stem cells to differentiate into replacement neurons. The aims of this project are to 1) determine the presence of MSCs in the olfactory mucosa, 2) compare olfactory MSCs with MSCs derived from the bone marrow and breast fat, known sources of MSCs.

PROGRESS:

1. Olfactory tissue cultures contain rare mesenchymal stem cells, compared with bone marrow and breast adipose cultures which are rich in mesenchymal stem cells.
2. Proteomic and antibody array analysis revealed that despite their differences in ability to function as mesenchymal stem cells, bone marrow, breast adipose and olfactory tissue cells demonstrated remarkable phenotypic similarity.
3. Meticulous examination and comparison of the proteomic and antibody array data from tissue cultures rich (bone marrow and breast adipose) and deplete (olfactory tissue) of mesenchymal stem cells, revealed new mesenchymal stem cell markers.

PROJECT TITLE: **Neurosteroids and Alzheimer's Disease: Protection against Beta-Amyloid Peptide-Induced Toxicity in Neuronal Cells**

RAC # 2080 005

INVESTIGATORS: *Dr. Fadia El-Bitar (PI), Dr. Chaker Adra, Dr. Yvette Akwa*

PROJECT DESCRIPTION: Alzheimer's disease is the most common cause of dementia in the elderly. The toxicity of β-amyloid (Aβ) peptides is thought to be involved in neuronal damage in this pathology. Our work is based on the use of natural pregnenolone sulfate (PREGS) which is one of the major neuroactive steroids produced in the central nervous system.

Our main objective is to investigate *in vitro* if PREGS has neuroprotective activity against Aβ peptide-induced neurotoxicity, using rat neuroblastoma B104 as cell culture model.

PROGRESS/ FINDINGS: We previously demonstrated (annual report of 2008) neuroprotective properties of PREGS against fibrillary form of human fAβ1–42 neurotoxicity. In the present work, we are examining the capacity of PREGS to correct soluble form of human sAβ25–35 neurotoxicity because this peptide fragment possess the most efficient toxic core related to Aβ1–42 peptide.

To achieve this goal, we showed the following:

1. The neurotoxicity of the soluble form of human sAβ25–35 peptide started to be induced on B104 cells at 5◂M after 6h treatment compared to control cells.
2. Most importantly, we demonstrated that PREGS was able to provide neuroprotection against sAβ25–35 neurotoxicity.
3. Thus, our results revealed neuroprotective activity of PREGS against both forms of peptides: fAβ1–42 and sAβ25–35.

Overall, treatment with a specific neuroactive steroid such as PREGS that counteracts the neurotoxic effects of Aβ peptide may be promising against neurodegeneration in Alzheimer's disease.

PROJECT TITLE: **Stem Cells Interactions with the Inflammatory Environment in Multiple Sclerosis and other Neurodegenerative Diseases of the Central Nervous System**

RAC # 2070 018 (MED 494–20)

INVESTIGATORS: *Dr. Chaker Adra (PI), Dr. Ayodele Alaiya, Dr. Imaduddin Kanaan, Dr. Samia Khoury, Dr. Joel Stern, Weassim Elyaman, Dr. Thamer AlKhairallah, Dr. Monther Al-Alwan, Kholoud Al-Saud (PhD Candidate)*

PROJECT DESCRIPTION:

AIMS OF THE STUDY

1. To examine the effect of Interferon (IFN)-gamma and the transcription factor STAT1 on the self-renewal program of Neural Stem Cells (NSCs) *in vivo* and on their molecular program *in vitro*.
2. To examine the effect of IFN-gamma on the migration of NSCs *in vivo* and on their molecular program *in vitro*.
3. To examine the effect of STATI on the differentiation of NSCs *in vivo* and on their molecular program *in vitro*.

METHODS: Several animal models will be used to determine the effect of STAT1 deficiency in NSCs in an inflammatory environment. This includes the use of STAT1 knockout mice and adaptive transfer of GFP-labeled STAT1-KO NSCs into wild type mice with Experimental Autoimmune Encephalomyelitis. To determine the effect of Interferon-gamma on NSCs migration *in vivo* in an inflammatory environment, IFN-gamma-KO GFP-labeled NSC will be adaptively transferred to wild type mice. Samples will also be subjected to proteome analysis using 2-DE, protein chips and mass spectrometry. Using these methods, the effect of STAT-1 and IFN-gamma genes on NSCs self-renewal capacity and migration will be assessed.

SIGNIFICANCE: Human embryonic stem cells represent great hope for successful treatment of diseases in the future including; Multiple Sclerosis, Alzheimer's Disease, Parkinson's Disease, Spinal Cord Injuries, Diabetes and Cardiovascular Disease. There is particular interest in using stem cells in the treatment of neurological disorders, because these injures are permanent due to the irreversibility of neuronal damage. In light of the lack of treatment for Multiple Sclerosis, the promise of stem cell therapy offers great hope in tissue repair, replacement and regeneration that will lead to new clinical innovations and revolutionize Personalized Medicare.

PROGRESS/ MAJOR FINDINGS:

1. The project was awarded KACST funding (#08-MED494–20)
2. An abstract and poster presentations accepted at 10th annual meeting of the International Society for Stem Cell Research, June 13–16, 2012, Yokohama, Japan. (*http://www.isscr.org/Annual_Meeting_Home.htm*).

PROJECT TITLE: **Proteomics Approach to Biomarker Discovery in Aplastic Anemia**

RAC # 2060 021

INVESTIGATORS: *Dr. Ayodele Abdulkareem Alaiya (PI), Dr. Mahmoud Al-Jurf (PI), Dr. Naeem Chaudhri (Co-PI) Dr. Hazzaa Al Zahrani (Co-PI) Dr. Mai Al-Mohanna, Dr. Entezam Sahovic, Dr. Fahad Al Mohareb, Dr. Fahad AL Sharif, Dr. Hamad Al Omar, Dr. Ali Al Shanqeeti,*

PROJECT DESCRIPTION: We will analyze global protein expression profiles in patients with aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH) and hypoplastic myelodysplastic syndrome (MDS). The goal is to identify novel protein biomarkers that can differentially diagnose various bone marrow failure syndromes and provide accurate patient stratification for treatment.

PROGRESS:

1. 2-DE gels for 18 samples have been completed including one sample each from either bone marrow and or peripheral blood from the same individual patients where possible.
2. Computer assisted image analysis of these samples has commenced.
3. Pending completion of complete pathological reports from our clinical collaborators to allow for detailed data analysis and result interpretations.
4. Our preliminary results show that the three-disease entities shares very similar protein fingerprints. (See Fig 4 for distribution of resolved protein spots on 2-DE)
5. We are in the process of conducting peptide mass fingerprinting by MALDI-TOF-MS and /or *de novo* sequencing (LC/MS/MS) for the identification of the differentially expressed proteins

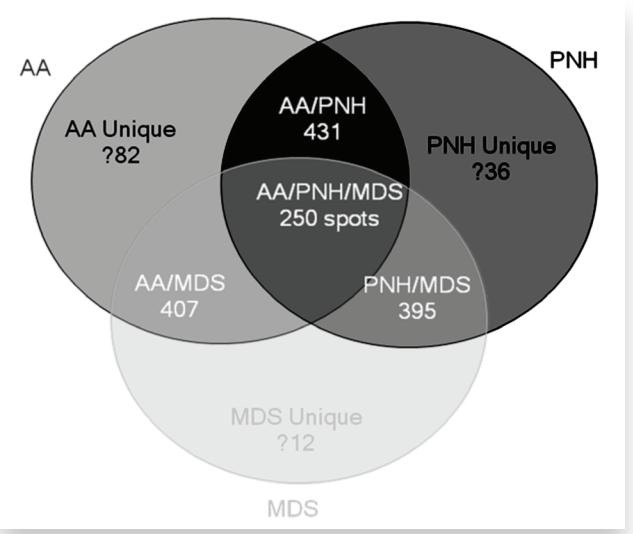


Figure 4: Distribution of total resolved protein spots resolved by 2-DE gel analysis across disease entities. Proteomics analysis can facilitate discovery of biomarkers that can rapidly become of outmost importance for early disease detection and individualized therapy.

PROJECT TITLE: **Clinical Proteomics: Development of Novel Biomarkers for Diagnosis of Ovarian Cancer**

RAC # 2050 043, Funded By KACST

INVESTIGATORS: *Dr. Ayodele Abdulkareem Alaiya (PI), Dr. Mai Al-Mohanna (Co-PI), Dr. Hany Al-Salem, Dr. Ismail Al-Badawi, Dr. Jamal Al-Subhi, Dr. Nada Al- Sahan, Dr. Asma Tulba MD, Dr. Osama Al-Omar*

PROJECT DESCRIPTION: The goal of this work is to develop tools for the accurate classification of borderline tumors and differential diagnosis of pelvic tumor of unknown primary origin. We are using mini-2-DE gels technology which are rapid, simple and sensitive, thus making it especially applicable for routine tumor diagnosis.

Protein spots that differ significantly in their expression between benign and malignant tumors will be identified and used for objective and accurate molecular classification of borderline ovarian tumors and in particular in the differential diagnosis of borderline tumors and carcinomas.

PROGRESS:

1. The final report was submitted and accepted by KACST in March 2011
2. The final report has been accepted by ORA
3. The identified differentially expressed proteins will be validated in archival materials
4. Manuscript in preparation.

PROJECT TITLE: **Chronic Myeloid Leukemia: Development and Validation of Therapeutic Hematoproteomic Biomakers**

RAC # 2050 040, (Proteomics)

INVESTIGATORS: *Dr. Ayodele Abdulkareem Alaiya (PI), Dr. Mahmoud Al-Jurf (Co-PI), Dr. Naeem Chaudhri (Co-PI), 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: This project focuses on the analysis of global protein expression profiles in patients with Chronic Myeloid Leukemia in the chronic phase (CP CML). Peripheral blood (plasma/serum) and bone marrow samples from the same patients will be analyzed using 2-D gel electrophoresis and computer-assisted image analysis. Proteins of interest will be identified by peptide mass fingerprinting and sequencing. The goal is to identify novel protein biomarkers that will predict therapy response or disease resistance. This information will assist clinicians to develop customized treatment plans for patients individually.

PROGRESS/FINDINGS:

1. Our preliminary data indicates that clinical and hematological responses at three months of Gleevec treatment can be predicted based on protein expression profiles of individual patients.
2. Sample collection is ongoing (43 samples have been collected so far). Chart review for extraction of clinical-pathological data for correlation of clinical features with protein expression patterns is ongoing for 3/6/12 month's treatment response.
3. Our results showed that bone marrow plasma proteome is more enriched than BM serum.
4. 2-DE gels for 24 samples have been completed including one sample each from either bone marrow and or peripheral blood from the same individual patients where possible.
5. Computer assisted image analysis of these samples has commenced. Pending completion of complete pathological reports from our clinical collaborators to allow for detailed data analysis and result interpretations.

PROJECT TITLE: **Clinical Cancer Proteomic: Understanding the Cellular and Molecular Biology of Prostate Tumors**

RAC # 2050 026

INVESTIGATORS: *Dr. Ayodele Abdulkareem Alaiya (PI), Dr. Ali Bin Mahfooz (Co-PI), Dr. Mai Al-Mohanna, Dr. Mohammad Aslam, Dr. Irfan Ahmed, Dr. Kamal Hanash*

PROJECT DESCRIPTION: The gene expression of prostate tumors at the protein level will be studied by means of 2-D gel electrophoresis and computerized image analysis. The focus of this project is on the complex protein expression pattern of human prostate tumors, of varying malignancy potential, to identify proteins related to tumorigenesis, grade of aggressiveness, metastatic potential and treatment sensitivity. The aim is to find a correlation between altered tissue morphology and polypeptide expression. Ultimately this would complement the diagnostic markers already in the use, and commence a wider scan of the prostate proteome for carcinoma specific markers. Novel proteins will be characterized by highly sensitive mass spectrometry and if necessary sequence analysis.

PROGRESS:

1. A final report of the study was approved by ORA and project was successfully completed.
2. Part of the findings was published in International Journal of Oncology titled "Proteomics -based Signature for Human Benign Prostate Hyperplasia and Prostate Adenocarcinoma"; Int. Jour. Oncol 38: 1047–1057, (2011)
3. This study validates protein-biomarkers that can be useful for accurate diagnosis and prognostic monitoring of prostate adenocarcinoma. Despite varied prevalence of the disease between different ethnic populations (i.e., high in Sweden, low in Saudi Arabia); the biomarkers indicate that BPH and prostate cancers are biologically 'homogeneous' in their protein expression patterns across wide geographical regions.
4. We plan to initiate collaboration with the Swedish group for possibility of validation of our findings using the combined samples from the two studied populations in Saudi Arabia and Sweden.

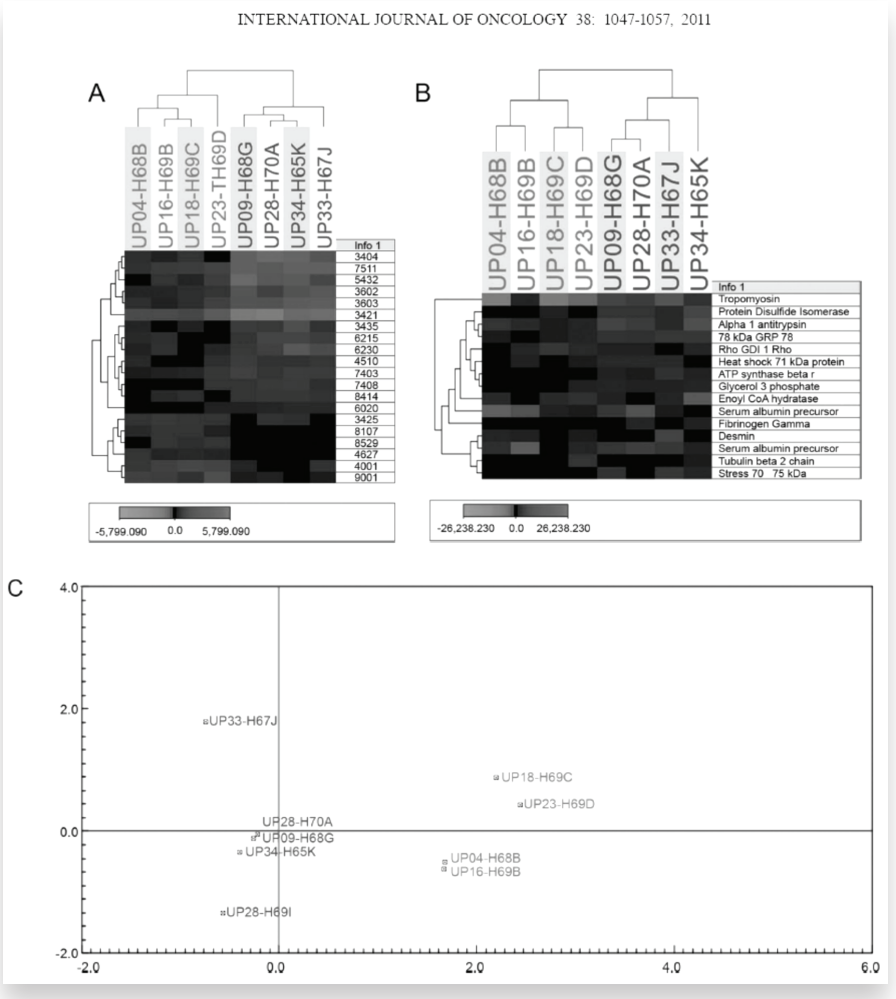


Figure 5: *(A)* Hierarchical Cluster analysis using the expression patterns of 20 proteins that are differentially expressed between Gleason 5 (low grade) and Gleason 7 (high grade) malignant prostate tumors. *(B)* Hierarchical Cluster analysis using the expression patterns of 15 proteins that have been identified both in this study and in previously published studies. The names of several of the identified proteins are indicated in the dendrogram (red, high grade Gleason 7; and blue, low-grade Gleason 5 cancers). The dendrogram was generated using the Bray Curtis distance metric and an average linkage clustering method from the J-Express software. *(C)* The correspondence analysis of the same dataset.

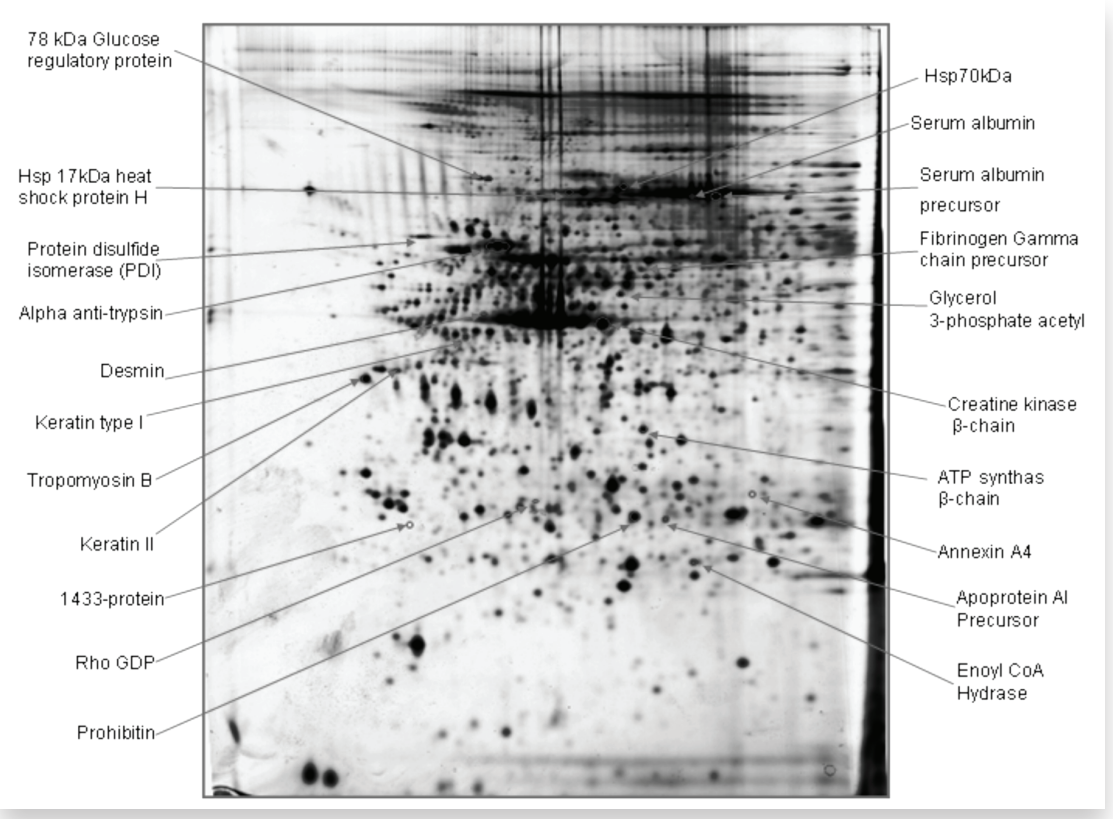


Figure 6: A representative 2-DE map derived from a prostate cancer sample. Marked are some of the identified proteins that differ between sample sub types. The proteins were identified by MALDI-TOF Mx Micro (Waters®, UK). Approx 80 % of the identified proteins in our study were found to be differentially expressed in in the published Swedish studies on prostate cancer.

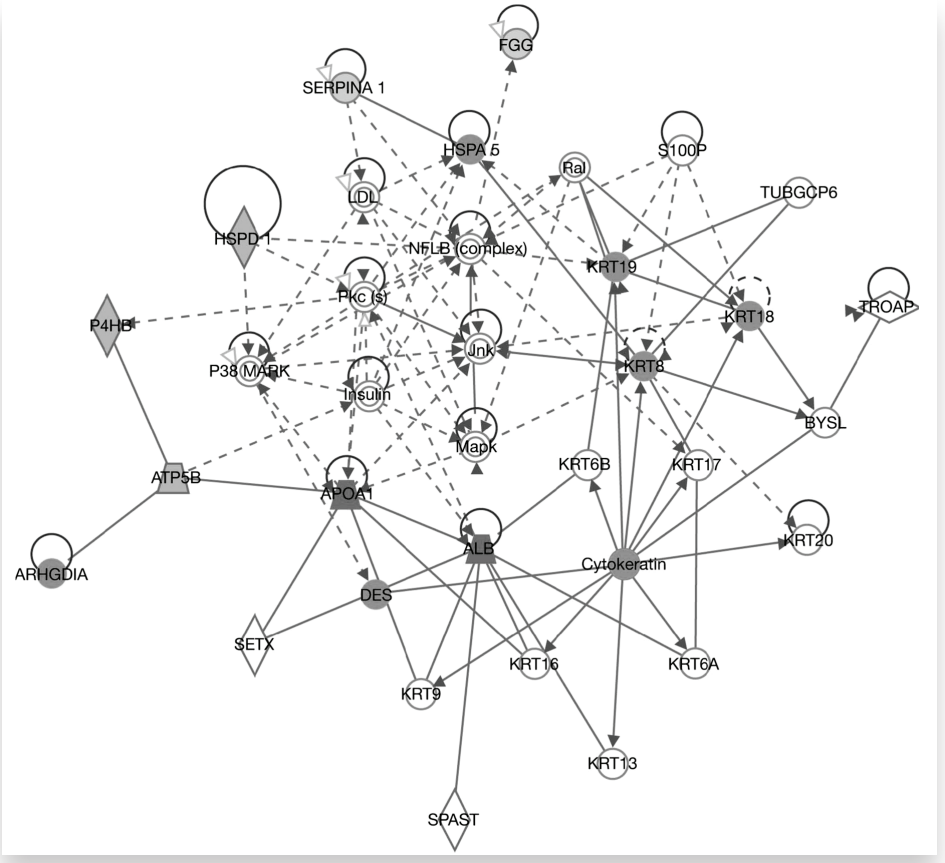


Figure 7: Canonical pathway analysis of network signaling of identified proteins in prostate cancer. Some of the identified proteins were mapped in Ingenuity database and represented in multiple sub-signalling networks and mostly regulates among others: proliferation, survival, cell cycle progression and apoptosis and these molecules are located mostly in the cytoplasm and only a few are located in the nucleus and extracellular space. While some of these molecules act as transporters, others act as enzymes and transcription regulators. The connection and the expression profile of some of the proteins are as indicated. Red indicates an up-regulated protein, and green color is indicative of down-regulation, a direct connection is by solid line and broken lines indicates an indirect interaction between different molecules ALB, albumin; APOA1, apolipoprotein A-I; ARHGDIA, Rho GDP dissociation inhibitor (GDI) α; DES, desmin; HSPA5, heat shock 70-kDa protein 5 (glucose-regulated protein, 78 kDa); KRT18, Keratin 18; KRT19, Keratin 19; KRT8, Keratin 8. The network analysis was done in Ingenuity Pathway Analysis program (IPA V8.7). Ref Alaiya et al, Int J Oncol. 38: 1047–1057, 2011.

PROJECT TITLE: **Protein Profiling: Understanding the Mechanisms of Tumor Responses to Therapy in a Mouse Model**

RAC # 2050 014

INVESTIGATORS: *Dr. Ayodele Abdulkareem Alaiya (PI), Dr. Mai Al-Mohanna, Dr. Raafat El-Sayed, Dr. Falah Al-Mohanna,*

PROJECT DESCRIPTION: This pilot study is based on a mouse 4T1 breast tumor model. The 4T1 mammary carcinoma cell line is transplantable and tumors grow both in nude and BALB/c mice and in tissue culture. In addition the cells give rise to tumors that are invasive and that easily metastasize to distant sites, thus mimicking human mammary cancer. Complex protein mixtures from tissue and serum samples will be analyzed from the same individual animal using 2 D gel electrophoresis and computer assisted image analysis. Proteins of interest will be identified by peptide mass fingerprinting and sequencing. The aim is to identify groups of proteins involved in the mechanism of tumor response to therapy.

PROGRESS:

1. Protein identification by MALDI-TOF MS from tissue and serum samples is was partly successful and we plan to use the LC/MS/MS approach for the identification of all the spots that were not successfully identified using the MALDI peptide mass fingerprinting.
2. Final report has been submitted to ORA.
3. Manuscript in preparation.

PROJECT TITLE: **Clinical Proteomics: Development of Novel Biomarkers for Translational Ovarian Cancer Research**

RAC # 2050 011

INVESTIGATORS: *Dr. Ayodele Abdulkareem Alaiya (PI), Dr. Mai Al-Mohanna (Co-PI), Dr. Ismail Al- Badawi, Dr. Hany Al-Salem, Dr. Jamal Al-Subhi, Dr. Nada Al- Sahan, Dr. Asma Tulba, Dr. Osama Omar*

PROJECT DESCRIPTION: This project focuses on the analysis of global protein expression profiles in patients diagnosed with sporadic common epithelial ovarian tumor that are treated with conventional surgical and adjuvant therapy and/or cytoreductive and radiation therapy. The goal is to identify novel protein biomarkers capable of predicting patient's response to therapy and clinical outcome.

PROGRESS:

1. Project have been successfully completed and final report submitted and approved by ORA
2. Manuscript is in preparation.
3. Validation of identified proteins will be done in large archival material. This will be conducted as a new project to be submitted to ORA.
4. Our findings showed that tumors of different malignant grades can be discriminated based on their protein expression patterns.
5. We are creating database for artificial disease classification of pelvic tumors based on differentially expressed proteins and efficient data mining as indicated in (figures 8 & 9).

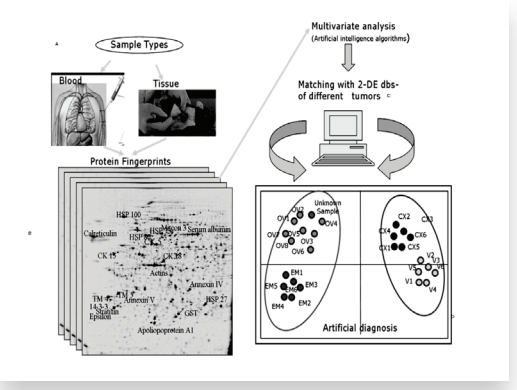


Figure 8. Schematic illustration of novel way of artificial tumor classification using multivariate data analysis of differentially expressed proteins. ***(A)*** Tissue or blood sample is processed, ***(B)*** Protein fingerprint is generated by 2-DE, ***(C)*** Fingerprint images are deposited in tumor database for expression analysis, ***(D)*** Computer assisted image analysis for artificial tumor classification.

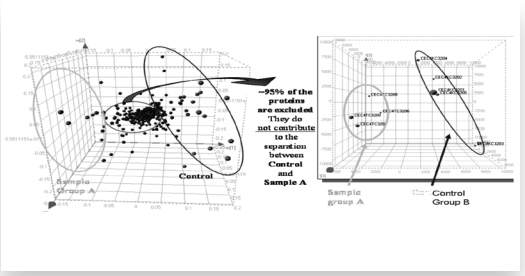


Figure 9. Our proposed data mining: Selection of significantly differentially expressed proteins that will be used for Molecular Classification of Tumors using Multivariate Analysis of Protein Expression Profiles.

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

INVESTIGATORS: *Dr. Monther Al-Alwan (PI), Dr. Hazem Ghebeh, Dr. Asma Tulbah, Dr. Taher Tweigeri, Dr. Dahish Ajarim, Dr. Mahmoud Al Jurf*

PROJECT DESCRIPTION: The cytoskeleton has been reported to regulate cell's morphology and motility. The actin-bundling protein, fascin, is a member of the cytoskeletal protein family. While it has restricted expression in specialized normal cells, many studies have reported fascin expression 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. A poster was presented at the Stem Cells, Cancer and Metastasis. Keystone, Colorado, USA (March 6–11, 2011) Monther Al-Alwan, Safiah Olabi1, Hazem Ghebeh, Eman Barhoush, Asma Tulbah, Taher Tweigeri, Dahish Ajarim, Ayodele Alaiya, Chaker Adra. Fascin regulates breast cancer invasion via modification of metastasis-associated genes.
2. An oral presentation was given at the International Conference on New Frontiers in Breast Cancer, Riyadh, Saudi Arabia (invited speaker - April 27–29, 2010). Al-Alwan M., Olabi S., Ghebeh H, Barhoush E, Tulbah A, Tweigeri T, Ajarim D, Alaiya A. and Adra CN. Molecular pathway of Cancer: Fascin mediates breast cancer metastasis via regulation of metastasis-associated genes.
3. Fascin regulation of breast cancer cell morphology, migration and invasion has been established
4. Inhibition of fascin in breast cancer cells by chemotherapy, leading to reduction in migration and invasion was observed.
5. Fascin regulation of breast cancer chemotherapeutic resistance has been observed.
6. Identifying the molecular mechanism of fascin regulation of breast cancer migration and invasion is ongoing.
7. Establishing the relationship of between fascin and stem cell phenotype and function.
8. A manuscript was published in PlOS ONE journal and another one is in preparation for submission.

PROJECT TITLE: **Proteomic analysis, anti-resorptive properties, and tumor cell cytotoxicity of osteodex in bone metastasis from breast and prostate cancer**

Proposal # 2080 052

INVESTIGATORS: *Dr. Ayodele A. Alaiya (PI), Dr. Chaker Adra (Co-PI), 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: Our main goal in this study is to demonstrate that our compound, osteodex (ODX) have a direct anti-tumor effect as well as indirect effect through the inhibition of osteoclasts thereby decreasing the amount of tumor growth promoting molecules in primary tumor as well as in bone metastasis. In order to achieve some of our objective we have done some *in vitro* experiments and currently the *in vivo* animal model experiments are in progress.

PROGRESS:

1. *In vivo* animal experiment is very encouraging. We observed significant differences in the tumor mass between tumor-bearing treated and untreated mice. We are awaiting the result of necropsy analysis.
2. Tissue samples has been collected and processed for 2-DE protein arrays. Preliminary gel analysis showed significantly differentially expressed protein spots between treated and non-treated tumor tissue samples.

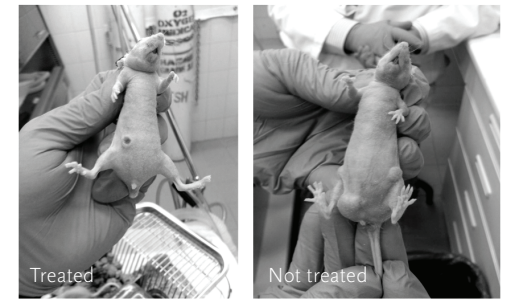


Figure 10. Physically the mice in the treatment group are much active with clean tumors. While the no treatment group are less physically active and many of them developed multiple tumors with massive ulcerations.

3. Preliminary results of *in vitro* experiment showed that Osteodex induced ~85–97% apoptosis at 10 ◂M in both breast MDA 231 and prostate PC3 cell lines, while the commercially available therapeutic agent Zometa failed to induce any significant apoptosis after 24 hrs treatments in any of the two cell lines at the tested concentration range (50 nM-10 ◂M) as shown in figure 2 below. Similar observation was observed at 48 hrs treatments (data not shown). Part of our findings on *in vitro* experiment resulted in one publication in *Int Journal Oncology 2010*

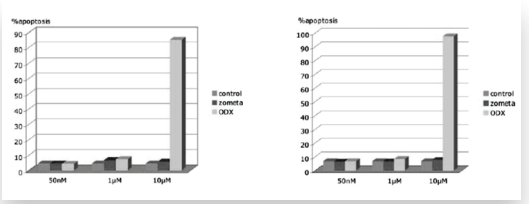


Figure 11. Effects of ODX and Zometa on treated PC3, MDA 231 and control cells: y axis = % apoptosis, x axis = concentration of test substance, mean values, n=2–3, cv=<10%.

Expression Proteomics

We treated cells with 10◂M for global protein expression profiles between control and treated cells. The 10◂M was chosen because it was the concentration that resulted in maximum effect of cell death in the apoptotic assay). Cells were treated with 10◂M for different time periods ranging from 3, 6, 18 & 24 hrs. Approximately 700 spots were resolved on 2-DE gels of which 62 spots were significantly differentially expressed and at least more than two-fold difference. (ANOVA, $p<0.05$).

The expression profiles demonstrated dose dependent changes among treated groups and clear separation from control untreated samples (Figure 12). A similar finding was observed in the PC3 prostate cancer cells (data not shown).

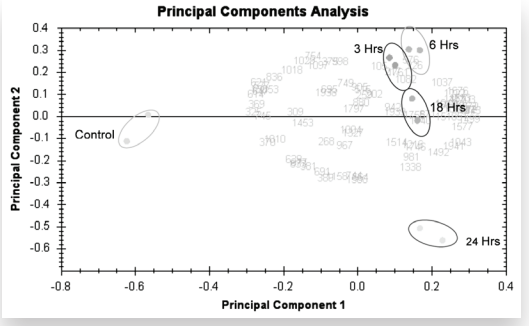


Figure 12. PCA analysis of differentially (< 2-fold change) expressed proteins between control cells and cell treated with different doses of ODX. (The observed different is significant by ANOVA, $P<0.05$).

SUMMARY: We have achieved part of the objectives of this study and have demonstrated the superior anti-tumor efficacy of our compound, osteodex (ODX) over one of the currently routine anti-cancer agents. We plan to do caspase analysis to validate the mechanism of the tumor cell killing properties of ODX and to complete *in vivo* studies to evaluate its possible clinical usefulness in breast and prostate cancers with bone metastasis.

PROJECT TITLE: **Study of the Association between HLA-DRB1 Alleles and Vogt-koyanagi-Harada's Disease in Saudi Patients**

RAC # 2050 034

INVESTIGATORS: *Khaled Al-Hussein and Khaled Tabara*

PROJECT DESCRIPTION: Vogt-Koyanagi-Harada (VKH) disease is a potentially blinding disorder that afflicts the uvea in the eye leading to chronic inflammation. Associations with other auto-immune disorders have been reported. In Saudi Arabia, VKH has been found to be a common cause of uveitis as previously reported by Islam and Tabbara. Previous reports indicate certain HLA genotypes show strong association with DRB1 *0405 and DRB1 *0410 and confer increased risk of VKH disease. It has been suggested that the HLA DRB1 gene is one of the candidate genes of VKH

PROGRESS, MAJOR FINDINGS:

1. The project was completed.
2. Two (2) papers have been published.

PROJECT TITLE: **Identification of HLA Alleles in Normal Saudi Individuals by Sequence Based Typing**

RAC # 2010 002 (AT-21 004)

INVESTIGATORS: *Khaled Al-Hussein and Abdelghani Tbakhi*

PROJECT DESCRIPTION: The major histocompatibility complex (MHC) also referred to as Human Leukocytes Antigens (HLA) has been linked to the development of most autoimmune diseases, cancer, susceptibility to infectious agents and most importantly allograft rejection. Until recently, much of what is known regarding the population genetics of HLA in Saudi Arabia has been derived from the application of conventional methods and the alleles identified in Northern European and North American populations. The frequencies of HLA alleles however, vary considerably among different ethnic groups. The conventional techniques used by most laboratories, including those in Saudi Arabia, for HLA tissue typing are incapable of detecting all allelic variations with precision without information on their DNA sequences.

PROGRESS: In this KACST approved project, 1000 healthy Saudi individuals, from various regions of the Kingdom of Saudi Arabia, was typed from their HLA allele using a valuable method known as Sequence Based Typing (SBT) whereby a spectrum of HLA Class I and II alleles was identified. This will facilitate the establishment of a Saudi HLA allele database. We have studied the frequency of HLA Class I (-A, -B, -C) alleles in 1000 normal Saudi individuals. Twenty-one HLA-A alleles were detected. HLA-A*0231 and HLA- A*3102/3104–5 were found to be the most frequent and the most diversified region in the HLA-Class I loci is the HLA-C Twenty-eight HLA-C alleles were detected.

PROJECT TITLE: **HLA Gene association in Patients with Type 1 Diabetes in Saudi Arabia**

RAC # 2000 029

INVESTIGATORS: *Khaled Al-Hussein and Mohammed Al-Ahmed*

PROJECT DESCRIPTION, PROGRESS AND MAJOR FINDINGS: Type 1 diabetes is an autoimmune disease caused by a combination of genetic, immunological and environmental factors. It is mediated by both CD4+ and CD8+ T cells and result in the destruction of beta islet cells in the pancreas. Since T cells see the antigen in the context of the MHC-antigen complex, immunogenetic studies are imperative to decipher the interaction of both humoral and cellular mediated interaction in the auto-destruction of beta islet cells. Previously (HLA) class II DQB1*0201/0202-

DRB1*04 genotype was reported to be a predisposing allele to type 1 diabetes {insulin-dependent diabetes mellitus (IDDM)} in the Saudi Arabian population, whereas significant protection was found to be conferred by DPB1*0401. Our reported data showed that high frequency of the DPB1*0104 allele, even in the presence of predisposing DQB1*2 allele, in healthy subjects may indicate a protective effect of this combination of HLA alleles against type 1 diabetes. In this project we used a larger cohort of control subjects and patients to confirm the above mentioned hypothesis that protective HLA class II genes can override the risk provided by HLA-DQ susceptibility alleles.

PROJECT TITLE: **Study of the relationship between the genetic polymorphisms of the Natural Killer Cell receptor (KIR) genes and the outcome of the hematopoietic stem cell transplantation for hematological malignancies in Saudi Arabia**

RAC # 2051 001 (KACST: AT-26–03)

INVESTIGATORS: *Mahamoud Al-Jurf, Abdelghani Tbakhi, Ameera Gaafar Mohamed, Khaled Al-Hussein*

PROJECT DESCRIPTION: Natural killer (NK) cells can mediate the acute rejection of bone marrow cell (BMC) allografts. The mechanisms underlying the rejection process remain unclear. NK cells express 1) inhibitory receptors specific for major histocompatibility complex (MHC) class I molecules and 2) activating receptors with diverse specificities. Inhibitory NK receptors confer to NK cells the ability to discriminate between MHC class I positive and negative target cells. Therefore they are involved in the control of NK cell tolerance to self and the elimination of cells that have down regulation of MHC class I molecules. Neither the KIR gene locus polymorphism nor the degree of KIR mismatch of our HLA donor-recipient transplant pairs has been identified in the Saudi population. Therefore, a prospective study that focuses on these two main aims is warranted. The purpose of this study is to investigate the effects of KIR incompatibilities in HLA- matched related donor-recipient pairs.

PROGRESS: The project was 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*

PROJECT DESCRIPTION: Transplantation is the ideal therapy for the majority of end-stage organ diseases. Organ transplantation, in Saudi Arabia, is a well-established modality in the treatment of organ failure. Genotyping profiles of the Natural killer cell Immunoglobulin-like receptors (KIR) have been reported to vary among different ethnic groups. This report represents a novel longitudinal study to investigate the underlying immune system genes, which contribute to graft survival or rejection in the Saudi population. New molecular markers will also be identified to predict the presence or absence of detrimental factors that underlay immune responses in clinical transplantation.

PROGRESS: The project was completed and two final reports submitted and accepted by KACST and ORA. In addition two manuscripts are currently being drafted.

MAJOR FINDINGS: Similar to most published data, we observed the dominance of the two framework genes 3DL2 and 3DL3which are present in all (100%) recipients and donors investigated so far. While the other KIR genes vary in their frequencies. We also observed the predominance of AA1 genotype. Allograft rejection was observed in 14 (19%) recipients. No association was observed of KIR genotypes with rejected or stable graft. In addition, a polymerase chain reaction with sequence-specific primers was used to screen for the known cytokines SNPs within genes encoding IFN-γ, TGF-β, TNF-α, IL-6 and IL-10 in the same set of donors/ recipients' pairs mentioned

above. We observed that low IL-10 productivity is positively correlated with stable graft. The project is progressing very well and almost 90% of its aims were fulfilled. Currently data is analyzed and a manuscript in preparation.

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

INVESTIGATORS: *Dr. Khaled Al-Hussein (PI), Dr. Hamad Al-Omar (PI), Dr. Ameera Gaafar, Dr. M. Al Jurf, Dr. A. Iqbal, Dr. A. Tbakhi, Dr. Fahad Al-Mohareb*

PROGRESS: The project was re-activated on the 11th of January 2011. An abstract was published in Exp. Hematol. and a manuscript is being prepared.

PROJECT TITLE: **A73 Gene in Nasppharyngeal Carcinoma and its Oncogenic Potential**

RAC # 2090 004

PRINCIPAL INVESTIGATOR: *Dr. Maha Al-Mozaini (PI), Dr. Mohammed Al-Ahdal, Dr. Asma Tulba*

PROGRESS: Submitted to ORA/KACST 30 December 2008. Almost half of the project is completed.

PROJECT TITLE: **Detection and Mutations within the UL97 Geme of Ganciclovir-Resistant Cytomegalovirus in Clinical Isolates**

RAC # 2090 003

INVESTIGATORS: *Dr. Maha Al-Mozaini (PI), Dr. Mohammed Al-Ahdal, Dr. Sahar Al-Thawadi, Dr. Sami Al-Hajar*

PROGRESS: Submitted to ORA/KACST, 2008 Dec. No. data yet.

PROJECT TITLE: **The Efficacy of Immunophenotyping and Molecular Studies in Improving Diagnosis, Sub typing and Management of Hematological Malignancies in Saudi**

RAC # 2080 053

PRINCIPAL INVESTIGATOR: *Dr. Saleh Al-Othman (PI), Dr. Chaker Adra (PI), Dr. Hussa Al-Hussaini, Dr. Mohammed Al-Dahmesh, Dr. Nasser Al-Thubiti*

PROGRESS:

1. REC Accepted and recommended the proposal for approval.
2. The proposal was forwarded to KACST as an Annual Grants Program. Unfortunately, it was not funded. Proposal was resubmitted for review by the scientific committee.

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

RAC # 2110 001 (P-L-11–0105)

INVESTIGATORS: *Dr. Maha Al-Mozaini (PI), Dr. Abdullah Al-Hokail, Dr. Mathias Lichterfeld, Dr. Chaker Adra, Dr. Xu Yu*

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

RAC # 2111 005 (A-N-11–0407)

INVESTIGATORS: *Dr. Maha Al-Mozaini(PI), Prof. Eric Rosenberg, Dr. Khalid Al-Meshari, Dr. Mathias Lichterfeld, Dr. Chaker Adra, Prof. Maria Davidian (Project Consultant), Prof. H.T. Banks (Project Consultant)*

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 (A-L 11–0425)

PRINCIPAL INVESTIGATOR: *Dr. Khaled Al-Hussein (PI), Dr. Chaker Adra, Dr. Fahad Al-Mohareb, Dr. Ameera Gaafar*

PUBLICATIONS

- Al-Alwan MM, Olabi S, Ghebeh H, Barhoush E, Tulbah A, Tweigeri T, Ajarim D, Adra CN. Fascin is a key regulator of breast cancer invasion that acts via the modification of metastasis-associated molecules. (*Plos One*. 2011;6(11):e27339.).
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- Al-Hujaily, EM; Mohamed, AG; Al-Sharif, I; Youssef, KM; Manogaran, PS; Al-Otaibi, B; Al-Haza'a, A; Al-Jammaz, I; Al-Hussein, K; Aboussekhra, A. PAC, a novel curcumin analogue, has anti-breast cancer properties with higher efficiency on ER-negative cells. *Breast cancer research and treatment* 2011;128(1):97-107.

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- Chaker Adra, Ayodele Alaiya, Lina Assad, Dania Alkhafaji, Zakida Shinwari, Zahi Nabi, Hadeel Al Manea, Ahmed Alshaikh, Osman Alfurayh, Lutfi Alkurbi, Edward Skolnik and Mamdouh Algaqumi, Proteomic Analysis of Class IV Lupus Nephritis: Global Versus Segmental (Submitted, *Journal of the American Society of Nephrology*, April 2011).
- Andrew Wetzig, Ayodele Alaiya, Monther Al-Alwan, Christian Benedict Pradez, Manogaran. S. Pulicat, Amer Al-Mazrou, Zakia Shinwari, Ghida Sleiman1, Hazem Ghebeh, Hind Al-Humaidan, Imaduddin Kanaan and Chaker Adra*. Towards Identification of Specific Mesenchymal Stem Cell Markers. (Submitted, *Stem Cells*). SC-11-0878.
- Hazem Ghebeh, Ghida Majed Sleiman, Pulicat S. Manogaran, Amer Al-Mazrou, Eman Barhoush, Asma Tulbah, Khalid Al-Faqeeh and Chaker Adra. Phenotypic characterization of normal human breast stem cells: A comprehensive profile (Submitted, *Stem Cells*). SC-11-09-18.
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MANUSCRIPTS IN PREPARATION

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- Gaafar A, Sheereen A, Iqneibi A, Mohamed G, Turpeinen H, Al-Mishari K, Al Hussain K. Association of different cytokines and cytokines gene polymorphism in kidney transplant recipients and their living related donors with rejection. (In preparation).
- 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. (In preparation).
- 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).
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ABSTRACTS

INTERNATIONAL SCIENTIFIC MEETINGS

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- Hazem Ghebeh, Ghida Sleiman, Eman Barhoush, Pulicant Manogaran, Taher Tweigeri, Khalid Al-Faqeeh, and Chaker Adra. Normal Breast has two phenotypically distinct bi-potent cell populations. 2010 Annual Research Report 25–26-April 2011, Prince Salman Auditorium, KFSH&RC, Riyadh KSA.
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- Ayodele A Alaiya, Mamdouh Albaqumi, Zakia Shinwari, Hamad Al-Mojalli, Hadeel Al-Manea, Dania Alkhafaji, Zahid Nabi, Ahmed Alshaikh, Mohamed Shukri, Osman Alfurayh, Lutfi Alkurbi, Edward Skolnik, Martin Pollak and Chaker Adra. Renal Proteomics: Identification and Validation of Protein Biomarkers for Classification of Focal Segmental Glumerulosclerosis and Lupus Nephritis. 2010 Annual Research Report, 25–26 April 2011, Prince Salman Auditorium, KFSH&RC, Riyadh KSA.
- Atia Sheereen, Ameera Gaafar, Alia Iqneibi, Abdelmoneim Eldali, Chaker Adra, Khalid F. Tabbara, Khaled Al-Hussein. Study of KIR genes and HLA-C in Vogt-Koyanagi-Harada Disease in Saudi Arabia. 2010 Annual Research Report, 25–26 April 2011, Prince Salman Auditorium, KFSH&RC, Riyadh KSA.
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PHD THESIS TITLE: **Serum Proteomic Analysis of Prostate Cancer Progression**

Jamal A. Al-Ruwaili

PROJECT DESCRIPTION: The reported incidence of prostate cancer (PCa) has increased in recent years due to the aging of the population and increased testing; however mortality rates have remained largely unchanged. Studies have shown deficiencies in predicting patient outcome for both of the major PCa diagnostic tools, namely prostate specific antigen (PSA) and trans rectal ultrasound -guided biopsy (TRUS). Therefore, serum biomarkers are needed that accurately predict prognosis of PCa (indolent vs. aggressive) and can thus inform clinical management.

AIM: This study uses surface enhanced laser desorption/ionization time of flight mass spectrometry (SELDI-TOF-MS) analysis to identify differential serum protein expression between PCa patients with indolent *vs.* aggressive disease categorised by Gleason grade and biochemical recurrence.

METHODS: A total of 99 serum samples were selected for analysis. According to Gleason score, indolent (45 samples) and aggressive (54) forms of PCa were compared using univariate analysis. The same samples were then separated into groups of different recurrence status (10 metastatic, 15 biochemical recurrence and 70 non- recurrences) and subjected to univariate analysis in the same way. The data from Gleason score and recurrence groups were then analysed using multivariate statistical analysis to improve PCa biomarker classification.

Using gel-electrophoresis technique, candidate biomarkers were separated and identified by LC-MS/MS and validated using optimised Western blot (WB) immunoassay against 100 PCa serum samples from the Wales Cancer Bank (50 as indolent group & 50 as aggressive groups).

MAJOR FINDINGS: The comparison between serum protein spectra from indolent and aggressive samples resulted in the identification of twenty-six differentially expressed protein peaks ($p<0.05$), of which twenty proteins were found with 99% confidence. A total of 18 differentially expressed proteins ($p<0.05$) were found to distinguish between recurrence groups; three of these were robust with $P<0.01$. Sensitivity and specificity within the Gleason score group was 73.3% and 60% respectively and for the recurrence group 70% and 62.5%.

Four candidate biomarkers (categorised by Gleason score) were identified using a novel 1 D LC-MS/MS technique. The candidate biomarker with m/z of 9.3 kDa was found to be up-regulated in aggressive PCa patients, and was identified as Apolipoprotein C-I (ApoC-I). Another three candidate biomarkers (22.2, 44.5 and 79.1 kDa) were found down-regulated in the aggressive group and up- regulated in the indolent group and identified as apolipoprotein D (ApoD), putative uncharacterised protein (PUP) and Transferrin (TF), respectively.

The utility of the putative biomarkers was examined by Western blot (WB) analysis of 100 blinded PCa serum samples.

This effort was reflected through two published paper entitled:

- Discovery of Serum Protein Biomarkers for Prostate Cancer Progression by Proteomic Analysis
- Proteomics in prostate cancer biomarker discovery

SCIENTIFIC CONFERENCE

This work was presented in NCRI cancer conference Liverpool, UK, 04–07 November 2011.

J Al-Ruwaili, SET Larkin, BA Zeidan, PA Townsend, CN Adra, CL Aukim-Hastie, Proteomic Profiling of Prostate Cancer Progression, Mar;7(2):93–103.

Also, it was presented in Molecular targets and mechanism of aging conference at USA, 2011.

Jamal Al-Ruwaili, Samantha ET Larkin, Bashar A Zeidan, Matthew G Taylor, Chaker N Adra, Claire L Aukim-Hastie, Paul A Townsend. Discovery of Serum Protein Biomarkers for Prostate Cancer Progression by Proteomic Analysis, June;7(2):20–101

PUBLICATION IN PREPARATION

FOUR PAPERS ARE IN PREPARATION FOR SUBMISSION

1. SELDI-TOF-MS Proteomics in Prostate Cancer. In preparation for submission to Expert Rev. *Proteomics*.
2. SELDI-TOF-MS technology in biomarker discovery of oncology. In preparation for submission to *Cancer Genomics and Proteomics Journal*.
3. Apolipoprotein C-I, Apolipoprotein D and Transferrin generated from SELDI-TOF-MS are not predictors of Prostate Cancer Progression in Prostate Cancer Patients; A Prospective Study in a Population at Risk. In preparation for submission to *Cancer Genomics and Proteomics Journal*.
4. Novel method for identification of serum protein biomarkers detected by SELDI-TOF -MS technology. In preparation for submission to *Cancer Genomics and Proteomics Journal*.

CHAPTER IN BOOK:

One chapter in book will be written in Prostate Cancer Proteomics to be included in the book Oncogenomics and Cancer Proteomics—Novel Approaches in Biomarkers Discovery and Therapeutic Targets in Cancer", ISBN 980-953-307-479-0, which is planned to be published in September 2012

STEM CELL THERAPY PROGRAM POST COCTORAL TRAINEES AND GRADUATE STUDENTS

POSTDOCTORAL TRAINEE

- Dr. Khaldoun Al-Romaih – Scholarship Program Harvard Medical School
- Dr. Maha Al-Mozaini – Scholarship Program Harvard Medical School

GRADUATE STUDENTS

- Kholoud Al-Saud. Obtained MSc (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 PhD The thesis was titled: Investigation of M-Phase Phosphoprotein (MPP11) as a novel target for Leukemia T Cell Immunotherapy. The degree was awarded with arrangment with University of Newcastle Upontyne, Newcastle Upontyne, United Kigndom.
- Layla Al-Mansouri. Started her PhD program in Stem Cell Therapy Program, Research Centre, and now she is presuming the degree in University of Toronto, Canada.

RESEARCH CENTRE TRAINING & EDUCATION OFFICE (RCTEO)

RESEARCH CENTRE TRAINING & EDUCATION OFFICE (RCTEO)

MANAGER
Huda Al Mosallam, MA

STAFF
Abdulrahman Al-Lahoo, *Coordinator*
Gina Rodil, *Hospital Assistant I*
Lama Sultan, *Hospital Assistant II*
Sara Abu Raad, *Hospital Assistant II*
May Fikry, *Department Secretary*
Nouf Al Ajmi, *Department Secretary*

THE RESEARCH CENTRE TRAINING AND EDUCATION OFFICE (RCTEO) was created in facilitating the following programs:

- In-Kingdom and Out-Kingdom scholarship training and education that lead to higher education. These programs support students to prominent institutions to certify with the advancement of technology.

- In-House & Al Faisal University Students Training in progressive fields of science and technology.

- Summer Training Programs such as:

  FUTURE SCIENTIST–a program that will assist talented young male high school Saudi nationals in acquisition of scientific skills and to prepare them for a future career in the field of Biomedical Sciences.
  IBN SENA–a program that will assist talented young Saudi nationals to integrate their scientific skills/talents to prepare them in different areas of Science in the future.
  AL-RAZI SUMMER PROGRAM is a program that will help the undergraduate students be exposed to the work environment and will give them the chance to get hands-on training in the basic science.

RC-TEO organizes and conducts Special Courses, Workshops, Symposia and other events throughout the year.

EXPERTISE

The RCTEO assists external training and education for Saudi citizens who wish to pursue MSc, PhD degrees and Postdoctoral Fellowship. Affiliations with reputable scientific and educational local and international institutions have been established to ensure that the latest technology is acquired hence, career development is advanced.

ACTIVITIES

The Research Centre Training and Education Office administer the following programs:

POSTDOCTORAL FELLOWSHIP PROGRAM

This is a program of study and research training at an institution abroad for Research Centre employees. The maximum duration of two (2) years should be relevant to the employees' work and the future direction of the Research Centre. This program is under the KFSH&RC scholarship guidelines.

Recipient	Total	Completed
Postdoc Fellow	4	

HOSPITAL SCHOLARSHIP PROGRAM

The Institution helps qualified employees to pursue their studies and obtain a higher degree or gain practical experience in their field, to serve the needs of KFSH&RC. The primary objective of this program is to raise the overall educational and healthcare standards at KFSH&RC by encouraging employees to develop their academic and technical skills. The scholarship can be given either as Out-of-Kingdom Study Program or In-Kingdom Study Program.

Recipient	Total	Completed (Cancelled)
PhD	19	3
MSc	8	(2)
BSc	4	0
Training	1	1

IN-HOUSE RESEARCH GRADUATE (FOR NON-RC EMPLOYEES)

This program is for MSc and PhD students from local or international universities who are interested in conducting their research project in the Research Centre under joint supervision with their university.

Research Student	Total	Completed
PhD	4	0
MSc	21	1

IN-HOUSE TRAINING PROGRAM FOR NON-RC EMPLOYEES (IHTP) & AL FAISAL UNIVERSITY STUDENT TRAINING (AFUTP)

The Research Centre provides training opportunities for eligible candidates from other institutions for a maximum of six (6) months. These include:

- Undergraduate students who are seeking training related to their university degree
- Individuals who are seeking training to enhance their qualifications.
- Saudi employees from public and private sectors who want to develop an aptitude for research.
- Recipients of fellowships sponsored by international institutions such as the International Atomic Energy Agency (IAEA) seeking on-the-job training.
- Medical Fellows/Residents for training in Research Methodology.
- High School students interested in a career in Biomedical Sciences can be given a short orientation.

Program	Completed
IHTP	142

FUTURE SCIENTISTS PROGRAM (FSP)

The aim of this program are to assist talented young male high school Saudi nationals in the acquisition of scientific skills, to help them appreciate science and its value to humanity, and to prepare them for a

future in the field of Biomedical Sciences by providing an environment for their scientific growth.

Program	Completed
FSP	14

IBN SENA PROGRAM (ISP)

An agreement was created in 2006 between KFSH&RC-Research Centre and King Abdulaziz and his Companions Foundations for Giftedness & Creativity to assist talented young Saudi nationals to integrate their scientific skills/talents to prepare them in different areas of Science in the future.

Program	Completed
ISP	32

AL RAZI SUMMER TRAINING PROGRAM (ARSTP)

The RC-TEO encourages cooperation with national institutes for the exchange of information and pursuit of knowledge in an organized and productive manner. The objective of this program is to expose the undergraduate students to the work environment and give them the chance to get hands-on training in the basic science and to show their abilities and find out their suitable field of science in the future.

Program	Completed
ARSTP	11

RESEARCH CENTRE SEMINARS (RCS)

Research Centre Training & Education Committee (RCTEC) represented by its office, organizes a weekly seminar to be given by Research Centre scientists. Special seminars also take place from time to time in the Research Centre through the close collaboration between the Office and the concerned Research Centre departments.

Program	Total	Attendees
RCS	23	954

WORKSHOPS, COURSES AND CONFERENCES (WS&CONF)

The Research Centre Training and Education Office assists in organizing a number of annual workshops, conferences and special courses/events in specific field of science.

Program	Total	Attendees
WS, C&Conf	5	366

MEDICAL AND CLINICAL AFFAIRS

DENTISTRY

CHAIRMAN

Abdulhadi Abanmy, BDS, DMSc

Pediatric Dentistry

RESEARCH ACTIVITIES

PROJECT TITLE: **Registry of Cleft Lip/Palate and Craniofacial Anomalies**

RAC # 991 030

INVESTIGATORS: *Dr. Aziza Al-Johar, Dr. Ali Al Mutlaq, Ms. Shazia Subhani*

PROJECT DESCRIPTION:

BACKGROUND: The King Faisal Specialist Hospital & Research Centre(KFSH&RC), established a cleft lip with or without cleft palate (CL/CP) registry and started collecting data on CL/CP patients attending the Department of Dentistry, KFSH&RC since mid-1999. The registry is a coordinated collaboration between the Department of Dentistry and Department of Biostatistics, Epidemiology and Scientific Computing (BESC). In 2003, the CL/CP registry is being expanded to include craniofacial anomalies in it scope and hence, the name of the registry is being changed from Cleft Lip/Palate Registry to Registry of Cleft Lip/Palate and Craniofacial Anomalies Registry.

RATIONALE: Treatment including multiple surgeries, speech therapy, and dental and orthodontics of cleft lip and palate have developed very rapidly, but the epidemiological study for cleft lip and palate remains in its infancy. The registry is an early warning system for discovering excessive occurrences of craniofacial anomalies and is the foundation for the epidemiological research needed to evaluate the clusters.

KFSH&RC is one of the major referral hospitals in the Kingdom. The development of a Craniofacial Anomalies Registry (in the absence of such a population-based registry) at KFSH&RC will be an important source of data on this congenital defect in the Kingdom. However, in the near future this will be a national registry.

PROGRESS: On-going project.

PROJECT TITLE: **Pattern of Craniofacial Anomalies Seen in a Tertiary Care Hospital, Riyadh, Saudi Arabia**

RAC # 991 030

INVESTIGATORS: *Dr Aziza Al-Johar, Dr Kandasamy Ravichandran, Ms Shazia Subhani*

PROJECT DESCRIPTION: Objective: To report the patterns of craniofacial anomalies in Saudi Arabia

DESIGN AND SETTING: Data from a hospital registry, based at a tertiary care center.

PATIENTS: Craniofacial patients registered during 2002–2008 in the Cleft lip/palate and craniofacial anomalies registry at King Faisal Specialist Hospital & Research Centre, Riyadh.

RESULTS: Out of the 411 craniofacial cases (M=223; F=188), 168 cases had cranial anomalies, 311 cases had facial anomalies with 68 cases overlapping both the conditions. Craniosynostosis, accounting to 33.1% of total cases, was seen in 75 male and 61 female. Out of the 66 cranial syndromic cases, Apert syndrome and Crouzon syndrome was seen in 25

and 18 cases, respectively. Among facial anomalies, Dysmorphic features were often observed (35) followed by protruded premaxilla (20) and micrognathia(18). Among facial syndrome, Pierre Robin sequence (66), Goldenfar syndrome (18) and Van der Woude syndrome(16) was observed. Among associated deformities of CL/P, cleft palate (160; 57.8%) was more common, followed by cleft lip and palate (87; 31.4%) and cleft lip (23; 8.3%). Out of the 208 cases having other congenital anomalies, cardiovascular is the most commonly affected system with 34 children. Significantly (p=0.01) more family history of anomalies was observed in children born to parents whose marriages among first cousin than in children born to parents whose marriages were not among first cousin.

CONCLUSION: The pattern of craniofacial anomalies observed in this study does not differ significantly from those reported in the literature.

PUBLICATION

Published in the *Saudi Medical Journal*, Sept 2011.

PROJECT TITLE: **Modeling Familial Aggregation of Cleft Lip/Palate: A Hospital Based Registry**

RAC # 2101 004

INVESTIGATORS: *Dr. Ravichandrean Kandasamy, Dr. Mohamed Shoukri, Dr. Yasmin Al Twaijri, Dr Aziza Al-Johar, Ms. Shazia Subhani*

PROJECT DESCRIPTION:

ABSTRACT: Several studies showed Cleft lip/palate (CL/P) are known to recur in families with the risk of having a second infant with CL/P after given birth to a first infant with same defect varies among women. A high risk of having infants with birth defects can result from maternal or paternal genes, dietary patterns, or long term exposure to environmental teratogens. A combination of genetic and environmental factors may cause a persistent risk of similar defects in siblings. There has been a considerable interest in specifying a genetic model that predicts the familial patterns of recurrence of CL/P. The best fitting single-locus model was found to be as good as the multifactorial threshold (MFT) model in explaining the family data on CL/P and isolated cleft palate collected in Hawaii. However, others showed neither the MFT model nor single-major locus (ML) with random environmental variation model provided a good fit. Genetic analyses of the probands' families were performed under the mixed model with ML and MFT components.

The proposed study is based on the data, without patient's identification detail, from the Cleft lip/palate and Craniofacial Anomalies Registry.

OBJECTIVES:

1. To examine similarity among pairs of sibling for each of the two traits (cleft lip or palate)
2. To assess elevation in the risk of disease for a single sib conditional of the fact that the other sib has attained the same disease condition, accounting for the within cluster correlation
3. To assess the possible effect of consanguinity and gender on the risk of cleft lip/palate.

METHOD: Maximum likelihood estimation method will be used to estimate the model parameters and standard errors of the estimates will be derived.

PUBLICATION: Published in the *American Journal of Medical Genetics*, 20 Feb 2011.

PROJECT TITLE: **Measurement of Treatment Outcome in the Cleft Lip and Palate Patients in King Faisal Specialist Hospital & Research Centre, Saudi Arabia**

RAC # 2091 017

INVESTIGATOR: *Dr Aziza Al Johar*

ABSTRACT: Cleft lip and palate is the most common birth defect worldwide. Clefts of the lip and/or palate (CLP) are a congenital anomaly and among the most common birth defects worldwide, presenting in

wide variety of forms and combination. The majority are non-syndromic where CLP occurs in isolation of other phenotypes. Cleft lip and/or palate consider syndromic when one or more additional features are involved.

The principal management of the KFSH interdisciplinary cleft team is to produce a child that looks normal, speak and hear normally with improved facial appearance. The team aimed at physical rehabilitation stressing the fact that the best treatment should ensure a good aesthetic and functional outcome.

The main purpose of this study is to evaluate the clinical outcome of the treatment of unilateral cleft lip and palate children who were treated at King Faisal Specialist Hospital since 1999, in order to improve quality of care.

SPECIFIC AIMS & OBJECTIVES

1. To evaluate the clinical outcome of cleft care at KFSH&RC
2. To identify risk factors for poor outcome
3. To address the health needs of these patients
4. To have periodic evaluation of cleft records and protocol

OBJECTIVES OF THE STUDY:

1. To examine existing records using different clinical too
2. To collect records of different clinical outcomes for cleft children
3. To compare the KFSH&RC's outcome result with the result from developed countries

METHOD: The study will be retrospective – case control study.

SAMPLE: The sample study population consist of 150 unilateral cleft lip and palate children who were treated at KFSH&RC from 1999 to 2007.

PROGRESS: On-going project

PROJECT TITLE: **Genetics of Craniofacial Birth Defects in Saudi Arabia**

RAC # 2080 006

INVESTIGATORS: *Dr Fouzan Al Kuraya. Dr. Aziza Al Johar*

ABSTRACT: Birth defects are important cause of disability worldwide with tremendous impact on the public health system. Craniofacial birth defects are particularly important because, as a group, they represent the second most common class of birth defects in humans. Additionally, they affect a region in the body that's readily observable by others thereby compounding the psychological component of the disability. The cause of most birth defects is unknown. Genetic, nutritional, infectious, and other environmental factors, contribute to the total incidence of birth defects, but the percentage attribute to each is not known. In Saudi Arabia several factors make it likely that genetic etiologies contribute more significantly to craniofacial birth defects than other parts of the world. Perhaps the most important of these factors is the high frequency of autosomal recessive disorders (many of which will inevitably involve the complex structure of the face and other craniofacial structures) as a result of high degree of inbreeding and consanguinity. One research group has an extensive experience in mapping mendelian disorders, including genetic conditions associated with craniofacial anomalies. Similarly, we have solid expertise in the areas of clinical, molecular and developmental genetics. We propose to focus our existing expertise direction of dissecting the molecular defects that underline craniofacial birth defects in Saudi Arabia. Characterizing these mutations will have an obvious impact on the medical care of the affected individuals since it makes prenatal/preimplantation diagnosis available options but it also represents a step in the right direction toward the implementation of gene therapy in conditions that are amenable to this approach. From an academic standpoint, the study of birth defects, craniofacial birth defects included, has proven indispensable to human genetics research. Biomedical literature is replete with high profile examples where the understanding of the genetic etiology of a given

birth defect was key to the discovery of highly important genes and pathways that propelled our understanding of how genes eventually control the making of a physical human being. Consequently, our group has a keen interest in understanding how different mutations affect the protein function of the respective genes. Furthermore, new genes identified in the course of this work represent an existing opportunity to better understand the molecular mechanisms that govern the formation of the craniofacial structures by studying their expression pattern and protein function. Given the scope of this project, the methodology will not only include linkage analysis but will also use the latest available tools in developmental and molecular genetics. This is a five year project genetic underlying defect.

AIMS OF THE PROPOSED STUDY:

1. To identify the genetic lesions (mutations) that underline the various genetic forms of craniofacial birth defects in the Saudi population.
2. To study the role of the identified genes in the model organism.

PROGRESS: On-going project

PROJECT TITLE: **The Incidence of Oral Mucositis in Pediatric Hematopoietic Cell Transplantation**

RAC # 2091 015

INVESTIGATORS: *Dr Zikra AlKhayal, Dr Mouhab Ayas, Dr. Mohammed Al Helal, Dr. Abdullah Al Jefri, Dr. Amal Al Seraihi, RN, Amal Mohammed*

PROJECT DESCRIPTION

ABSTRACT: Oral Mucositis is one of the most common and debilitating forms of Mucositis and often arises from high dose chemotherapy and radiotherapy. It is reported that seventy to eighty percent of patients undergoing hematopoietic cell transplantation (HCT) suffer from oral Mucositis during cancer therapy. The objective of the study is to evaluate prospectively the incidence of oral mucositis in pediatric patients aged 0 to 14 years receiving myeloablative conditioning regimens and hematopoietic cell transplantation at the bone marrow transplant unit at King Faisal Specialist Hospital & Research Centre. The results of the study will address the extent of oral mucositis in the bone marrow transplant unit and if there is a need for future management plans to improve the quality of life and provide optimal care for this special group of pediatric patients.

SPECIFIC AIMS AND OBJECTIVES:

1. To assess prospectively the incidence of oral mucositis in the pediatric population receiving hematopoietic cell transplantation (HCT) at King Faisal Specialist Hospital & Research Centre-Riyadh.
2. To evaluate the factors predicting oral mucositis severity and correlation with disease category, conditioning regimen, type of transplant and delayed absolute neutrophil recovery.
3. The outcome of oral mucositis and relation between grade severity, reported pain, ability to eat, saliva production and analgesic use.

METHOD: The study will be a prospective cross-sectional, case-control study.

PATIENTS: The sample study population will consist of all pediatric patients age 0 to 14 years old undergoing hematopoietic cell transplantation at King Faisal Specialist Hospital & Research Centre during the study period October 2009-October 2010.

PROGRESS: On-going

PROJECT TITLE: **The propagation of mesenchymal and neural stem cells from adult olfactory mucosa**

RAC # 2080007

INVESTIGATORS: *Dr Chaker Adra (PI) and Dr Zikra AlKhayal*

PROJECT DESCRIPTION

ABSTRACT: Recent investigations into the treatment of spinal cord injuries using stem cell therapy have shown promising results. The majority of studies

utilize non-neural tissue as a source of stem cells. In particular, mesenchymal stem cells have been utilized in transplantation experiments to treat animal modes of neural disorders. Upon transplantation mesenchymal stem cells allow function improvement by providing immunosuppressive and neurotrophic support. However, mesenchymal stem cells, largely, fail to differentiate when transplanted. The humal olfactory epithelium is an accessible source of stem cells. The lamina propria of the olfactory mucosa contains mesenchymal tissue that may contain a neural stem cell population. As an inherently neural stem cell population, olfactory neural stem cells may be more likely to differentiate into appropriate neural phenotypes upon transplantation than non-neural stem cells. Therefore, the human olfactory mucosa may be a source of both neural stem cells and mesenchymal stem cells for therapeutic use.

HYPOTHESIS: Both neural and mesenchymal stem cells can be derived from the human adult olfactory mucosa using animal serum free techniques.

AIMS

1. To determine the presence of mesenchymal stem cells in the olfactory mucosa.
2. To develop animal serum free techniques for the culture of mesenchymal stem cells with mesenchymal and neural stem cells from the adult olfactory mucosa.
3. To compare olfactory mesenchymal stem cells with mesenchymal stem cells derived from the bone marrow and umbilical cord examining their specific protein "fingerprint".

METHODS: The study will use cell isolation and isolation of mesenchymal stem cells from olfactory mucosa.

PROGRESS: Ongoing.

Prosthodontics

PROJECT TITLE: **Gene Expression & Immuno-Histological Findings in Patients with Papillon Lefèvre Syndrome**

RAC # 2070 022

INVESTIGATORS: *Adeeb Al Omrani BDS, DMSc (PI) Namik Kaya, PhD (Co-PI), Saleh Al-Muhsen, MD Dilek Colak, PhD, Hamad Al Zaidan, MD Said Dermime, PhD, Mohammed Al Owain, MD Hazem Ghebeh, PhD, Richard Hakansson, DDS, PhD, Christer Ullbro, DDS, PhD*

PROJECT DESCRIPTION

ABSTRACT: Papillion-Lefebvre syndrome is an autosomal recessive disorder characterized by hyperkeratosis of palm and soles and by a generalized aggressive periodontitis and premature loss of primary and permanent dentition. It is relatively prevalent in a small village north of Riyadh with more than 60 patients being followed in the dental clinic at KFSH&RC. Severe periodontal disease plays an important role in PLS resulting in premature loss of primary and permanent dentition. Two mutations have been identified in the cathepsin C (CTSC) gene in this population. The aim is to study the histopathology, immunological profile, and gene expression of PLS from blood samples and gingival biopsies; and thus shed more light on the pathophysiology of the disease and explore whether new subclasses of this disease can be identified based on gene expression profiles. Furthermore, we aim to establish a preventative program among this high-risk group through carrier testing and genetic counseling. The study will include 40 PLS patients presented at the dental department in KFSH&RC, retrospectively. A correlation may be found between the immunological status/gene expression and level/severity of periodontal infection. This may give more insight on the role of cathepsin C in the disease.

AIMS: Our aim in this study is to perform a thorough genetic and immunological evaluation in a cohort of Saudi patients with PLS from the following aspects:

1. COMPREHENSIVE GENETIC ASSESSMENT
   - Gene expression profiling of PLS patients, carriers and controls in the blood and patients, and controls in gingival tissue.
2. STUDY THE IMMUNOLOGIC STATUS OF PLS FROM BLOOD SAMPLES
   - Detailed neutrophils function including: adhesion (by means of CD11/CD18 expression) chemo taxis, phagocytosis and killing abilities (by evaluating the oxidative burst function).
   - Lymphocytes phenotypic distribution, and lymphocytes proliferation assays.
   - Natural Killer cytotoxic activity.

PROGRESS: On-going.

PROJECT TITLE: **Rare dental disorder registry**

RAC # 2071082

INVESTIGATORS: *Dr Abeeb Al Omrani (PI), Dr Hans Hansson, Dr Richard Hakansson, Dr Khalid Al Zoman, and Ms Shazia Naz Subhani*

PROJECT DESCRIPTION

ABSTRACT: Congenetal oral anomalies are a broad category of health conditions that are present at birth and are a deviation from normal anatomic growth, development, or function. There is an urgent need to increase knowledge about oral rehabilitation for people with oral/dental disabilities and new methods for treatment must be developed and evaluated. This will lead to better care and will have great influence on the quality of the quality of life for people with oral disabilities.

AIMS: The aim of this registry is with a multi-disciplinary team approach enhancing the opportunities for individuals with rare-oral and facial disorders to get adequate information, dignosis and treatment at King Faisal Specialist Hospital & Research Centre, from all over the country.

PROGRESS: On-going.

Periodontics

PROJECT TITLE: **Serum Levels of Leptin, C-reactive Protein and Pro-Inflammatory Cytokines: Their Relationship to Periodontal Health and Disease in Saudi Periodontitis Patients**

RAC # 2111 065

INVESTIGATORS: *Dr. Khalid Al Zoman, Dr. Sultan Mubarak, Dr. Hussein Naif, Dr. Ali Al Ghamdi*

PROJECT DESCRIPTION

ABSTRACT: Metabolic syndrome is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes. Periodontal disease is associated with the components of Metabolic syndrome, such as obesity, diabetes, hypertension and hyperlipidemia. Therefore, strong relation with periodontal disease and metabolic syndrome is suggested. Because both periodontitis and the metabolic syndrome are associated with systemic inflammation and insulin resistance, these two diseases may be linked through a common pathophysiologic pathway.

Leptin, a non-glycosylated polypeptide hormone, has been classified as a cytokine. Leptin and its receptor share structural and functional similarities with members of the long chain helical cytokines: interleukin-6, interleukin-11, interleukin-12, leukemia inhibitory factor, granulocyte-colony–stimulating factor, and oncostatin M. Thus, leptin might be classified as a cytokine. Circulating leptin in humans is mainly secreted from adipose tissue. It has been suggested that leptin orchestrates the host response to inflammatory and infectious stimuli as it induces the production of cytokines and allows for the phagocytosis of macrophages. Thus, the overall increase in leptin during inflammation and infection indicates that leptin is part of the immune response and host defense mechanisms.

Several studies have reported an association between severity of periodontitis and leptin levels in serum or gingival crevicular fluid (GCF). Karthikeyan et al reported that leptin levels decreased progressively in GCF as periodontal disease progressed.

Recently, it has been suggested that leptin plays a significant role in bone formation by virtue of its direct effect on osteoblast proliferation and differentiation, and in prolonging the life span of human primary osteoblasts by inhibiting apoptosis. Leptin is also involved in antiosteogenic effects by acting centrally on the hypothalamus. Thus, leptin at high local concentrations protects the host from inflammation and infection and maintains bone levels.

PURPOSE: The purpose of this study is to investigate the effects of the periodontal treatment on the serum levels of leptin and other cytokines in Saudi patients with chronic periodontitis (CP).

PROGRESS: On-going.

PROJECT TITLE: **A Prospective Observational Multicenter Cohort Study to Assess the Incidence of Osteonecrosis of the Jaw (ONJ) in Cancer Patients with Bone Metastases Starting Zoledronic Acid Treatment**

RAC # 2111 094 (S0702)

INVESTIGATORS: *Dr. Waled Rasheed, Dr. Kausar Suleman, Dr. Khalid Al Zoman*

PROJECT DESCRIPTION

PURPOSE: The purpose of the study is to learn how often ONJ occurs in patients who are being treated with zoledtronic acid during a 3-year time period after starting treatment. This study will also identify risk factors associated with ONJ.

OBJECTIVES:

1. To prospectively assess the cumulative incidence of osteonecrosis of the jaw (ONJ) at 3 years in cancer patients with bone metastasis receiving zoledronic acid treatment.
2. To describe the clinical presentation and natural history of ONJ.
3. To identify potential risk factors for the development of ONJ.
4. To estimate the cumulative incidence of ONJ at 3 years for different tumor types (breast cancer, multiple myeloma, prostate cancer, lung cancer and other cancers).
5. To investigate potential predictive and/or prognostic markers of increased risk for ONJ and/or to explore the potential mechanism of ONJ, the following correlative science resource banks will be established:
   - A specimen bank of serum for banking and whole blood for DNA analysis
   - A serial imaging bank of available x-rays, scans, CT's and MRI's for ONJ cases, as well as for a set of non-ONJ controls.
6. To better define the patient-related outcomes of ONJ in those patients who develop ONJ.

STUDY DESIGN: This is a SWOG (Southwest Oncology Group) study.

PROGRESS: On-going.

EMERGENCY MEDICINE

EMERGENCY MEDICINE

CHAIRMAN
Taimur Butt, MD

RESEARCH COORDINATOR & CONSULTANT
Hameed Ullah Khan, MD

MANY PROJECTS WARE UNDERTAKEN DURING 2011 BY DOCTORS working in the Department of Emergency Medicine. Five research projects are still in progress whereas two projects were completed and published.

DETAILS OF THE RESEARCH ACTIVITIES

PROJECT TITLE: **Does population in the Riyadh city, Saudi Arabia have the knowledge of burn prevention and first aid treatment?**

RAC # 2121 068

PRINCIPAL INVESTIGATOR: *Mohammed Al Omar, MD*

OBJECTIVE: There are two objectives to this study. The study will try to find out the knowledge of Riyadh City population of burn prevention and if they know first aid treatment of the burn.

DESIGN: Cross sectional study survey

SETTING: Riyadh Saudi Arabia

STUDY POPULATION/ SAMPLE: Randomly selected sample of people of Riyadh

PROJECT TITLE: **Do we need a focused teaching to optimize educational objectives of residence during their pediatric emergency rotation?**

RAC # 2121 017

PRINCIPAL INVESTIGATOR: *Narges Daliri, MD*

OBJECTIVE: The objective of the study is to try to find out if the needs of the residents training are met during their pediatric emergency rotation and whether we need more focused approach to meet their needs.

DESIGN: Cross sectional

SETTING: Pediatrics Emergency Medicine Department King Faisal Specialist Hospital

STUDY POPULATION/ SAMPLE: All the resident coming to Emergency Medicine department until required sample size is completed

PROJECT TITLE: **What is the Hydration Status of Emergency Department Physicians and Nurses by the End of Their Shift?**

INVESTIGATOR: *Mohammed Al Omar.*

Objective: To find out whether there is a difference in the hydration status of Emergency medicine staff King Faisal Specialist Hospital and Research Centre before and after their shift.

DESIGN: Cross sectional analytical study

SETTING: Emergency Medicine Department King Faisal Specialist Hospital and Research Centre.

STUDY POPULATION/ SAMPLE: Physicians and nursing staff of the Emergency Medicine Department King Faisal Specialist Hospital and Research Centre.

PROJECT TITLE: **Correlation between venous, arterial blood gas samples in Emergency Department patients**

RAC # 2101 066

PRINCIPAL INVESTIGATOR: *Abdulaziz Alrajhi, MD*

OBJECTIVE: The objective of the study is to correlate the values of Venous Blood Gas and Arterial Blood Gas sampled taken at the same time.

DESIGN: Cross sectional analytical study

SETTING: Emergency Medicine Department King Faisal Specialist Hospital and Research Centre.

STUDY POPULATION/ SAMPLE: All patients who will need Arterial Blood Gas during the period of study

PROJECT TITLE: **Title: Accuracy of acetaminophen dosing in children by caregivers in Saudi Arabia**

INVESTIGATORS: *Mohammed Alomar, Fawaz Alenazi, Nahar Alruwaili*

OBJECTIVE: The objective of this study was to determine if caregivers give children with fever an accurate dose of acetaminophen and determine factors associated with dosing inaccuracy.

DESIGN: Cross sectional

SETTING: ED of a tertiary referral center over a 6-month period (March–August 2008)

STUDY POPULATION/SAMPLE: We interviewed 200 caregivers who gave acetaminophen to children with fever in the preceding 24 hours.

MAIN RESULTS: Of 200 caregivers, 178 (89%) were included in the study. Seventy-six caregivers (43%) gave an accu-rate dose of acetaminophen, 54 (30%) gave a subtherapeutic dose, and 48 (27%) gave supratherapeutic doses. Caregivers who gave accurate doses were more likely to give an acetaminophen dose in less than a 4-hour frequency (risk ratio [RR] 0.63. P<.04, 95% CI, 0.37-1.07). Patients receiving acetaminophen per rectum had a significantly greater rate of supratherapeutic doses than those receiving the drug by mouth (9/28 [32%] versus 39/149 [26%]), respectively (95% CI=0.14 to 0.48). Sixteen caregivers (9%) gave more than five doses per 24 hours (RR, 1.11; 95% CI, 0.74-1.67). Physicians, pharmacists, and parents (the latter with intermediate and sec-ondary levels education) more often gave inaccurate doses, but the differences were not statistically significant suggesting that they may be the source of inaccurate dosing. (RR, 1.29; 95% CI, 0.95-1.75), (RR, 1.27 95% CI, 0.75-2.18), (RR, 1.28; 95% CI, 0.91-1.79), and (RR, 1.20, 95% CI, 0.92-1.57), respectively.

CONCLUSION: More than half of caregivers gave an inaccurate dose of acetaminophen to children suggesting that education may be valuable in ameliorating this common problem.

PROJECT TITLE: **Title: Diagnostic coding of abuse related fractures at two children's emergency departments**

INVESTIGATORS: *Zeeshanefatema Somjia, Amy Plint, Candice McGahernb, Ahmed Al-Salehd, Kathy Boutisa*

OBJECTIVE: The primary objective of this study was to determine the proportion of fracture cases investigated in the ED for abuse that had corresponding International Classification of Diseases (ICD) codes documenting abuse suspicion. Additional objectives were to determine the proportion of these fractures with admission ICD abuse coding, and physician text diagnoses recording abuse suspicion in the ED and/or admission notes. Factors possibly associated with abuse-related ED ICD codes were also examined.

DESIGN: Retrospective study

SETTING: Department of Pediatrics, Division of Emergency Medicine, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada Department of Pediatrics, University of Ottawa, 401, Ottawa, ON, Canada Department of Emergency Medicine, University of Ottawa, 401, Ottawa, ON, Canada Department of Emergency Medicine, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia Study population/ sample: Children less than three years of age that presented primarily with a fracture to two large academic children's hospitals from 1997 to 2007 and were evaluated for suspicion of abuse by child protective services were included.

MAIN RESULTS: Of the 216 eligible patients, only 23 (11.5%) patients had ED ICD codes that included the possibility of abuse. Forty-nine (22.7%) had the possibility for abuse documented by physicians as an ED discharge diagnosis. In addition, 53/149 (35.6%) of all admitted patients and 34/55 (61.8%) of confirmed abuse cases included abuse-related admission ICD coding. Female gender was found to be a factor associated with ED ICD abuse codes.

CONCLUSION: Current standards of ICD coding result in a significant underestimate of the prevalence of children assessed in the ED and hospital wards for possible and confirmed abusive fracture(s).

PROJECT TITLE: **A cross sectional survey to assess the safety of dispensing prescribed iron formulation in child resistant containers among pharmacies in Riyadh City, Saudi Arabia**

INVESTIGATOR: *Nahar Al Ruwaili, MD*

OBJECTIVES:

1. To know if iron is dispensed in child-resistant containers;

2. To emphasize the importance of using child-resistant containers.

DESIGN: A prospective cross sectional observational study.

SETTING: Assessing the proper dispensing of ferrous sulfate tablets in child-resistant containers from major city pharmacies.

STUDY POPULATION/SAMPLE: Pharmacists dispensing iron in Major pharmacies in Riyadh.

MAIN RESULTS: Forty (40) governmental and private pharmacies were visited. Ferrous sulfate with a total of 1800 mg elemental iron package was the most commonly found. None from the pharmacies dispensed iron in child-resistant containers.

CONCLUSION: All pharmacies dispensed iron in non child-resistant containers. Public Health efforts on increasing awareness and improving packaging are highly needed.

Authority regulations to use child-resistant packaging for retail packages of elemental iron are required.

FAMILY MEDICINE & POLYCLINICS

FAMILY MEDICINE & POLYCLINICS

CHAIRMAN
Abdullah Alkhenizan, MD

THE DEPARTMENT OF FAMILY MEDICINE AND POLYCLINICS ENHANCE the staff productivity in terms of clinical and academic aspects through revitalization of the Department Research Committee. Also, with the provision of greater incentives to do research studies, a good number of proposals were submitted. Collaborations with other departments are in progress in order to translate the clinical data into research studies that will enhance the physicians' standards of patient care in King Faisal Specialist Hospital & Research Centre.

RESEARCH ACTIVITIES

PROJECT TITLE: The Role of Gene Polymorphism in the Regulation of the Thyroid Stimulating Hormone Levels

RAC #2100 025

INVESTIGATORS: *Nduna Dzimiri, PhD (PI), Ali S. Alzahrani, MD (Co-PI), Maha Al Rasheed, Ms Pharm, Abdulraof Ahmad Al Mahfouz, MD, Jalal Jalaluddin, PhD, Abdullah Alkhenizan, MD*

PROJECT TITLE: **Detection of Interferon Gamma Production for the Diagnosis of Latent Tuberculosis in Healthcare Workers at KFSH&RC**

RAC # 2091 046

INVESTIGATORS: *Sahal Al Hajoj, PhD (PI), Abdulrahman Al Rajhi, MD (PI), Ali Alzahrani, MD, Sahar Al-Thawadi, MD, Abdullah Alkhenizan, MD, Abdulaziz Al Saif, MD, Kevin Hafez, MD, Haifa Al-Talhi*

PROJECT TITLE: **An Observational Epidemiological Study on the Prevalence of Human Papilloma Virus (HPV) Types in Women Older Than 15 Years of Age in the Kingdom of Saudi Arabia**

RAC # 2091 096

INVESTIGATORS: *Ishmail Badawi, MD (PI), Tarfah Muammar, MD*

PROJECT TITLE: **A Survey on Folic Acid Use and Knowledge in a Saudi Pregnant Population**

RAC # 2111 027

INVESTIGATORS: *Patricia McWalter, MD (PI), Amal Alshmmasi, MD*

PROJECT TITLE: **Significance of Hypovitaminosis D in Saudi Population: A Single Center Experience**

RAC # 2111 030

INVESTIGATORS: *Aneela Hussain, MD (PI), Abdullah Alkhenizan, MD, Mohammed El-Shaker, MD, Hussain Raef, MD*

PROJECT TITLE: **Chronic Disease Registry**

RAC # 2111 046

INVESTIGATORS: *Aneela Hussain, MD (PI), Abdullah Alkhenizan, MD*

PROJECT TITLE: **Attitudes Towards HPV Vaccination in Primary Care Clinic of KFSH&RC, Saudi Arabia**

RAC #2111 107

INVESTIGATORS: *Aneela Hussain, MD (PI), Abdullah Alkhenizan, MD, Nusrat Qazi, MD, Amal Alshmassi, MD, Patricia McWalter, MD, Samina Farooqi, MD, Ahmed Abdulkarim, MD*

PROJECT TITLE: Does Vitamin D Reduce Risk of Developing Type 2 DM in Pre-Diabetics? A Double-Blind Randomized Controlled Trial.

RAC # 2101 040

INVESTIGATORS: *Mohammed Hammami, MD (PI), Mohammed El Shaker, MD, Syed Alvi, H. Amer*

PUBLICATIONS

- Impact of Accreditation on the Quality of Health Care Services: A Systematic Review of the Literature. Abdullah Al Khenizan, MD and Prof. Charles Shaw. *Annals of Saudi Medicine* 2011 Jul–Aug; 31(4):407-16.
- Toward Excellence in Health Care: A Call for the Saudi Center for Health Excellence. Abdullah Alkhenizan, MD and Tawfiq Khoja, MD. *J Family & Community Medicine* Dec 2011, Vol 18, Issue 3; 99–100.
- Case Report: Swyer-James-Macleod Syndrome in a Sixty Year Old Patient. Patricia McWalter, MD and Amal Alshmassi, MD. *Iraqi J. Comm. Med.*, Oct 2011, Vol 24(4):361-363.

- Updated Recommendations for the Diagnosis and Management of Osteoporosis: A Local Perspective. Hussein Raef, Munira Al Bugami, Sakra Balharith, Mahmoud Moawad, Mohammed El Shaker, Aneela Hussain, Ahmad Al Shaikh, Ismail Badawi. *Ann Saudi Med* 31(2) March-April 2011; p111-128.
- Saudi Hypertension Management Guidelines 2011. Osman Alfurayh, Abdullah Alkhenizan, et al. King Fahad National Library.

HEART CENTRE

HEART CENTRE

DIRECTOR
Jehad Al Buraiki , MD

The heart centre is committed to excellence in patient care, teaching, and research. Its mandate includes research on the challenges of cardiovascular diseases facing the people of Saudi Arabia and its objective is to increase scientific knowledge of cardiovascular diseases, including their epidemiology, risk and risk factors, prevention, detection and diagnosis, treatment and prognosis, and to initiate cardiovascular, evidence-based programs.

In 2011 the Heart Centre had 35 approved/ongoing research projects. These projects included prospective study, retrospective records review and analysis, registries, interventional, diagnostic, basic research. All sections of the Heart Centre have research proposals as follows: Adult Cardiology = 11, Adult Cardiovascular Surgery = 5, Pediatric Cardiology = 9, Pediatric Cardiovascular Surgery = 5, Adult and Pediatric Cardiovascular Surgery = 4, Adult and Pediatric Cardiology =1.

The Heart Centre continues to develop its Strategic Research Plan (SRP) which is designed to develop and sustain significant, internationally acknowledged research in several thematic areas relevant to the high incidence of cardiovascular diseases in the Kingdom. The Heart Centre plans to significantly increase its research capacity in each of these areas over the next five years and to become recognized internationally for its high caliber research.

RESEARCH ACTIVITIES

PROJECT TITLE: **Central Venous Oxygen Saturation (Scvo2)/ Lactate Ratio As A Predictor of Major Adverse Event After Pediatric Cardiac Surgery: A Prospective, Observational Study**

RAC # 2101 061

PRINCIPAL INVESTIGATOR: *Makram Habib, MD*

PROJECT DESCRIPTION: The aim of this study is to assess whether Central venous oxygen saturation (Scvo2)/lactate ratio is a reliable predictor of hospital mortality and major adverse event after pediatric cardiac surgery.

PROGRESS: Ongoing.

PROJECT TITLE: **Congenital Heart Disease Registry**

RAC # 991 026

PRINCIPAL INVESTIGATORS: *Mansour Al Joufan, MD / Zohair Al-Halees, MD*

PROJECT DESCRIPTION: This Registry is a collaborative project between the Heart Centre and the Biostatistics, Epidemiology and Scientific Computing Department, Research Centre to collect data on pediatric patients with congenital heart disease and published annual report.

PROGRESS: This Registry is on-going. The cumulative number of subjects enrolled is 23338.

PROJECT TITLE: **Pediatric Heart Catheterization Registry**

RAC # 2001 053

PRINCIPAL INVESTIGATOR: *Fadel Al Fadley, MD*

PROJECT DESCRIPTION: The aim of this Project is to establish a registry for all diagnostic and interventional pediatric cardiac catheterizations performed at the KFSH&RC.

PROGRESS: This is an ongoing Registry. The cumulative number of subjects enrolled is 3981. The number of subjects enrolled during the last approval year is 454.

PROJECT TITLE: **Valve Registry**

RAC # 2001 055

PRINCIPAL INVESTIGATOR: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: This Registry includes data on KFSH&RC patients (both adult and pediatric) who underwent valve surgery. Data on these patients' pre-operative, peri-operative, post-operative and follow-up course, including data on events such as thromboembolism, endocarditis, rhythm variations, anticoagulation, anticoagulation-related bleeding, readmissions, re-operations, symptomology and medications has been collected.

PROGRESS: This is an ongoing Registry. The cumulative number of subjects enrolled is 7853. The number of subjects enrolled during the last approval year is 240.

PROJECT TITLE: **Percutaneous Trans Luminal Coronary Angioplasty (PTCA) Registry**

RAC # 2001 057

PRINCIPAL INVESTIGATOR: *Hani Al Sergani, MD*

PROJECT DESCRIPTION: This is an on-going Registry of patients who underwent Percutaneous Trans luminal Coronary Angioplasty (PTCA) at the KFSH&RC. The objective is to examine revascularization strategies for coronary artery disease and the outcomes of interventions for patients with acute coronary syndrome and chronic coronary insufficiency.

PROGRESS: This is an ongoing Registry. The cumulative number of subjects enrolled is 3980.

The number of subjects enrolled during the last approval year is 345.

PROJECT TITLE: **KFHI Surgery Registry**

RAC # 2001 058

PRINCIPAL INVESTIGATOR: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: This Registry includes all cardiovascular surgical procedures performed at the KFSH&RC and is utilized as a valuable research and program administrative tool.

PROGRESS: This is an on-going Registry. The cumulative number of subjects enrolled during the lifetime of the Project is 31521. The number of subjects enrolled during the last approval year is 1300.

PROJECT TITLE: **The Short and Long Term Effect Of BT Shunt Size On The Outcome After First Palliative Surgery**

RAC # 2111 014

PRINCIPAL INVESTIGATOR: *Raja Said Abou El Ella, MD*

PROJECT DESCRIPTION: The aim of this study is to compare the impact of different BT shunt sizes on patient outcome.

The outcomes will be divided into:
SHORT TERM: ICU and hospital stay, and mortality (up to 6-month after surgery).
LONG TERM: pulmonary artery pressures and branch pulmonary artery growth pre-Glenn surgery.

PROGRESS: Data has been reviewed and collected for 89 patients. Data analysis is in progress.

PROJECT TITLE: **Assessment Of Mitral Valve Area By Transthoracic 2-Dimensional And Doppler Echocardiography In Patients with Rheumatic Mitral Stenosis**

RAC # 2111 032

PRINCIPAL INVESTIGATOR: *Mohammed Amri, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective study. The echocardiographic reports of 150 patients who were studied with standard transthoracic echo/Doppler are being reviewed. The aim of this study is to compare and validate three different noninvasive techniques for valve area calculation in patients with mild, moderate or severe mitral stenosis.

PROGRESS: 150 patients have been enrolled. Statistical analysis is in progress.

PROJECT TITLE: **Is Myomectomy Justifiable In Preventing Recurrence Of Discrete Subaortic Obstruction?**

RAC # 2031 072

PRINCIPAL INVESTIGATOR: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: This is a retrospective study of patients with atrioventricular valve regurgitation who underwent a modified Fontan operation from 1986 to 2001 at the KFSH&RC. The aim of the Study is to compare the recurrence of sub aortic obstruction in patients with or without of myomectomy for discrete sub aortic stenosis.

PROGRESS: Ongoing. 156 patients have been enrolled.

PROJECT TITLE: **Permanent Pacemakers Post Cardiac Surgery In Adult Patients: Indications And Predictors**

RAC # 2101 035

PRINCIPAL INVESTIGATOR: *Bandar Al Ghamdi, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective, comparative study. The medical records of adult patients who underwent cardiac surgery, from January 01, 1999 to June 30, 2009, are being reviewed.

PROGRESS: Data from 1266 patient records has been reviewed. Currently, ECGs for these patients are being assessed (minimum of three EKGs per patient).

PROJECT TITLE: **The Impact Of The Right Ventricular To Pulmonary Artery Shunt on The Early Outcome of The Modified Norwood Procedure**

RAC # 2041 041

PRINCIPAL INVESTIGATOR: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: This retrospective review is studying the outcomes of patients with right ventricle to pulmonary artery shunt who underwent a modified Norwood Procedure.

PROGRESS: 126 patients were enrolled in this study. Final Report: The Sano shunt as the source of pulmonary blood in a Norwood procedure results in stable hemodynamics, however this may be on the expense of developing pulmonary vascular disease if the Glenn Shunt is not performed early. The Sano shunt should be utilized selectively and the procedure done earlier rather than later.

PROJECT TITLE: **Electrocardiogram Screening for School Children: A Cross- Sectional, Population Based Study**

RAC # 2101 092

PRINCIPAL INVESTIGATOR: *Majid Al Fayyadh, MD*

PROJECT DESCRIPTION: The objective of this study is to assess whether an ECG performed during childhood may contribute to the early identification of subjects at risk of cardiovascular morbidity and mortality, particularly disease whose prognosis may be significantly improved by an adequate therapy. Additionally, the prevalence, the clinical significance and the characterization of ECG abnormalities will be determined in a large population of children.

PROGRESS: The logistics for conducting this study in 36,000 children has been planned, equipment purchased, and staff hired. The project will begin in September 2012 at the start of the school year.

PROJECT TITLE: **Long-Term Outcome of Mitral Valve Repair Versus Mitral Valve Replacement Using Mechanical and Bioprosthetic Valves**

RAC # 2051 016

PRINCIPAL INVESTIGATOR: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: This retrospective review is studying the long-term effect of mitral valve repairs versus mitral valve replacement using mechanical and/or bio prosthetic valves.

The aims of the study are to:

1. Compare the event-free survival periods associated with mitral valve repairs and replacement.
2. Describe the incidences of redo repairs and redo replacements.
3. Identify the factors contributing to the need for redo surgeries, and
4. Study the above factors on mortality and morbidity.

PROGRESS: The data has been cleaned and validated on approximately 779 patients who meet the Study criteria. Follow-up data collection on enrolled patients is ongoing.

PROJECT TITLE: **Permanent Pacing in Pediatric Patients: The King Faisal Specialist Hospital Experience**

RAC # 2051 040

PRINCIPAL INVESTIGATOR: *Majid Al Fayyadh, MD*

PROJECT DESCRIPTION: This is a retrospective review to evaluate the experience and long term results of pacemaker (PM) therapy in children treated at the KFSH&RC.

PROGRESS: A permanent pacemaker was implanted in 385 patients. Subgroups were evaluated and reported accordingly. A Final Report has been submitted.

PROJECT TITLE: **SAUDI AF SURVEY (SAS): National, Observational, Cross Sectional Survey Evaluating The Atrial Fibrillation Management and The Cardiovascular Risk Profile of AF Patients**

RAC # 2111 021

PRINCIPAL INVESTIGATOR: *Bandar Al Ghamdi, MD*

PROJECT DESCRIPTION: This is a prospective Study to investigate the disease management of patients with atrial fibrillation in daily medical practice and to identify cardiovascular risk profile of AF population. The identification of the incidence and prevalence of a disease in the region is the first step in identifying its burden and effects on the society and a beginning in reaching the best management strategies and approach, and a registry of any disease in Saudi Arabia would not be complete without including the population being treated at the KFSH&RC. The results of this study may help to optimize the care and consolidate specialized resources required for the care of atrial fibrillation patients.

PROGRESS: Enrolled 25 patients in the study. Data collection completed and it is in the process of analysis.

PROJECT TITLE: **Incidence and Complications of Anemia in Children Undergoing Corrective Surgeries at the KFHI for Non-Cyanotic Heart Disease**

RAC # 2111 064

PRINCIPAL INVESTIGATOR: *Abdullah Alwadai, MD*

PROJECT DESCRIPTION: This is a retrospective, chart review study. The medical records of pediatric patients who underwent cardiac surgeries between March 2010 and February 2011will be reviewed. Aim of the study is to determine the incidence and main risk factors for anemia in pediatric patients going for cardiac surgeries at the KFHI. Also to study the post-operative complications in pediatric patients with or without anemia who underwent cardiac surgery at the KFHI and to determine if there is a correlation between pre-operative anemia and specific post-operative complications.

PROGRESS: Enrolled 143 patients in the study and team is completing the data collection and sending for data analysis .

PROJECT TITLE: **Prosthetic Valve Endocarditis in Adults: A Review of Early and Late Outcomes at the KFHI**

RAC # 2101 020

PRINCIPAL INVESTIGATOR: *Shahid Khan, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective comparative study of patients who underwent surgery associated with endocarditis from January 01, 1995 to August 30, 2009. The aims of this study are to determine the incidence, risk factors, outcome, associated morbidity and mortality of patients with prosthetic valves who develop endocarditis.

PROGRESS: 107 patients were enrolled; data collection is ongoing.

PROJECT TITLE: **The Role of Tracheostomy in Weaning Adult Post Cardiac Surgery Patients Off Mechanical Ventilators: A Non-Randomized, Retrospective, Comparative Study**

RAC # 2111 002

PRINCIPAL INVESTIGATOR: *Aly Makram Habib, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective, comparative study. The medical records of all adult patients who underwent cardiac surgery and had mechanical ventilation for 7 days or more post-surgery starting from 2008 to 2011 will be reviewed.

PROGRESS: Ongoing.

PROJECT TITLE: **A Randomized, Prospective Study to Compare Outcomes Following Diuresis with and without ACE Inhibitors in Acute Decompensated Heart Failure**

RAC # 2101 043

PRINCIPAL INVESTIGATOR: *Waleed Al Habeeb, MD*

PROJECT DESCRIPTION: This is a prospective study. Patients with chronic heart failure on maintenance ACEI/ARBs admitted with acute decompensated HF and with stable blood pressure will be enrolled and divided into 2 groups. Group 1 will have ACEI/ARBs held during admission and Group 2 will continue on their medications. The patients will be evaluated

on admission and on Day 4 and the results will be compared.

PROGRESS: Ongoing.

PROJECT TITLE: **PREMIER (Pulmonic Valve Replacement Multi-Discipline Emea Registry)**

RAC # 2111 043

PRINCIPAL INVESTIGATOR: *Zohair Al Halees, MD*

PROJECT DESCRIPTION: This is an international, multi-center, prospective, consecutively enrolled, observational registry. The purpose of this registry is to expand upon existing data sets, to identify patient characteristics and indicators related to complications and clinical benefits for symptomatic patients with a regurgitant or stenotic pulmonary valved conduit undergoing treatment with the commercially available Edwards SAPIEN XT™ Valve, and delivery devices.

PROGRESS: Ongoing

PROJECT TITLE: **Panorama: An Observational Study**

RAC # 2061 075

PRINCIPAL INVESTIGATOR: *Majid Al Fayyadh, MD*

PROJECT DESCRIPTION: This Study is collecting epidemiological data on patients who have Medtronic implantable pulse generators and implantable cardioverters/defibrillators.

The aims of this post-marketing study are to:

1. Investigate the long-term operation of the devices and device features;
2. Assess the frequency and duration of heart-failure related hospitalizations;
3. Analyze temporal aspects of cardiovascular events and symptoms;
4. Describe the incidence and prevalence of ventricular and atrial arrhythmias;
5. Associate cardiovascular events and symptoms with device data and diagnostics;
6. Determine programming preferences considering physical assessment variables and pathologies;
7. Build a prognostic model of time to death by using population baseline variables as predictors.

PROGRESS: 71 patients have been enrolled. Follow-up will continue for 5 years.

PROJECT TITLE: **The Heart Ejection Assessment Registry Trial In Saudi Arabia (HEARTS)**

RAC # 2101 025

PRINCIPAL INVESTIGATOR: *Waleed Al Habeeb, MD*

PROJECT DESCRIPTION: The aims of the HEARTS registry are to assist in reducing the gap between research and practice and hence to improve the quality of cardiac care for all patients with heart failure in Saudi Arabia.

PROGRESS: Fifty (50) patients have been enrolled. Enrollment and data collections are ongoing.

PROJECT TITLE: **Prevalence of Coronary Artery Disease in Patients Undergoing Heart Valve Surgery at KFHI: A Non-Randomized, Retrospective Study**

RAC # 2101 026

PRINCIPAL INVESTIGATOR: *Shahid Khan, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective study. The medical records of all adult patients who underwent pre-surgical cardiac catheterization and mitral and/or aortic valve repair or replacement surgery from January 01, 2005 to January 30, 2010, are being reviewed . The aim of the study is to assess the prevalence of coronary artery disease in patients with/without a history of rheumatic fever who underwent cardiac cath pre-mitral and/or aortic valve replacement or repair surgery.

PROGRESS: Ongoing.

PROJECT TITLE: **Retrospective Analysis of Patients Profile Having Intravascular Hemolysis in the Prosthetic Heart Valves: Experience At KFSH&RC**

RAC # 2111 088

PRINCIPAL INVESTIGATOR: *Naveed Akhtar, MD*

PROJECT DESCRIPTION: This is a descriptive, retrospective study. The medical records of all patients who underwent ultra-filtration for the treatment of diuretic-resistant, recurrent, acute decompensated heart failure from 01 January 2007 to 30 June 2011are being reviewed. The aim of this study is to report the KFSH&RC experience of using ultra filtration as an effective treatment to remove fluid overload in patients with diuretic-resistant, decompensate, congestive heart failure.

PROGRESS: Ongoing.

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

RAC # 2111 109

PRINCIPAL INVESTIGATOR: *Naveed Akhtar, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective, comparative study. Medical records of all adult patients over the age of 14 years, who underwent heart valve surgery in the form of replacement or repair or have been following Heart Centre, KFSH&RCRiyadh, after valve surgery elsewhere, are being reviewed. The aims of the study are to determine the factors associated with development of haemolytic anaemia in patients with heart valve surgery. Also the association of hemolysis with type and position of the valve.

PROGRESS: Ongoing.

PROJECT TITLE: **A Non-Randomized, Retrospective Study to Compare the Clinical & Cost Effectiveness of Surgical Debridement & Delayed Primary Closure with Conservative Management of Post-Cardiac Surgical Wounds**

RAC # 2081 014

PRINCIPAL INVESTIGATOR: *Sajjad Yousafzai, MD*

PROJECT DESCRIPTION: The aim of this study was to compare aggressive surgical debridement & delayed primary closure with the conservative management of wounds healing by secondary intention in order to evaluate the clinical effectiveness & cost effectiveness of the two methods.

PROGRESS: 30 Patients were enrolled in the Study. Conclusion: Compared with conservative treatments, aggressive surgical debridement under local anesthesia with delayed primary closure is an efficient, cost & clinically effective option with better cosmetic outcome.

A Final report was submitted.

PROJECT TITLE: **Re-Ly AF Registry: Risk Factors, Treatments and Outcomes for Emergency Department Patients with Atrial Fibrillation in Multiple Regions of the World**

RAC # 2081 033

PRINCIPAL INVESTIGATOR: *Bandar Al Ghamdi, MD*

PROJECT DESCRIPTION: Due to variations in medical practice and access to care, there is geographical variation in presentation and management of patients with atrial fibrillation. The aims of the study are:

1. To determine variations in the predisposing conditions for atrial fibrillation and atrial flutter (AF/flutter) between different regions of the world and practice settings
2. Document regional variations in the management of AF/flutter and associated cardiovascular disease, including the frequency of anti-thrombotic and anti-hypertensive therapy and the degree of INR control and
3. To document differences in the adverse cardiovascular outcomes of AF/flutter.

PROGRESS: One hundred twenty one (121) subjects have been enrolled Follow-up data collection is ongoing.

PROJECT TITLE: **Mechanical Tricuspid Valve Replacement at the King Faisal Heart Institute**

RAC # 2101 094

PRINCIPAL INVESTIGATORS: *Shahid Khan, MD*

PROJECT DESCRIPTION: This is a non-randomized, retrospective study. The medical records of patients who underwent tricuspid valve replacement using mechanical valve prosthesis at the Heart Centre are being reviewed.

The aims are to:

1. Assess the short and medium term outcome of patients undergoing mechanical tricuspid valve replacement
2. Assess the effect of mechanical tricuspid valves on right ventricular function, and
3. Describe the incidence of thromboembolic complications related to mechanical tricuspid valves.

PROGRESS: Ongoing

PROJECT TITLE: **Characteristics of Sudden Death (SD) in Qassim**

RAC # 2081 070

PRINCIPAL INVESTIGATOR: *Majid Al Fayyadh, MD*

PROJECT DESCRIPTION:

The aims of this Research are to:

1. Identify the incidence of unexpected, witnessed and unwitnessed SD victims in a Saudi community.
2. Identify the medical characteristics of unexpected witnessed and unwitnessed SD victims in a Saudi community.
3. Study the outcome of unexpected witnessed and unwitnessed SD victims in a Saudi community.

PROGRESS: We identified 180 deaths and completed data collection. The final report showed: SD represents 17 % of the total causes of mortality in the region studied; SD was the leading cause among all causes identified: 37% of the SDs occurred in people under the age of 40 years.

PROJECT TITLE: **Normal Ventricular Dimensions and Function in Newborns by Three-Dimensional Transthoracic Echocardiography (3D Echo)**

RAC # 2081 091

PRINCIPAL INVESTIGATORS: *Ziad Al Bulbul, MD*

PROJECT DESCRIPTION: This Study was conducted to determine the usefulness of 3D echo in assessment of ventricular dimension and function in newborns without the need for general anesthetic or sedation.

The aims of the study were to:

1. Establish the normal volume measurements of the left and the right ventricle in the newborn by 3D echo.
2. Compare the 3D right ventricle volume and function measurements in newborns from the 4 chamber or a subcostal window measurement.
3. Evaluate the practicality of the 3D echo in measuring the volume and the function of (RV) and (LV) without sedation.

PROGRESS: 36 patients were enrolled in the study and the study was successful. Further development in Echo technology is on its way to clinical practice, that is pertinent to our project, that which to investigate in the future.

PROJECT TITLE: **Genetics of Mandelian Cardiovascular Disorders in Saudi Arabia**

RAC # 2080 032

PRINCIPAL INVESTIGATORS: *Majid Al Fayyadh, MD/Zuhair Al-Hassnan, MD*

PROJECT DESCRIPTION: In this project, we aim at identifying genes responsible for Mendelain Cardiovascular Disorders (MCD) in our population. This will provide molecular characterization of patients with known syndromes as well as those with novel non-described phenotypes. The identification of the underlying genes will provide major practical information. The molecular data allows us to confirm the clinical diagnosis and can be used as a parameter for risk stratification to tailor the therapeutic approach accordingly. Due to the fact that some of the MCD are characterized by incomplete penetrance, the important contribution of mutation detection to patient management is the identification of asymptomatic carriers and hence, implementing prophylactic management. In addition, genetic counseling and appropriate preventive interventions can be offered.

PROGRESS: Ongoing. Recruited 199 patients and family members with various forms of Mendelain cardiovascular disorders. Conducted genome-wide analysis and homozygosity mapping for 36 families with recessive dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), or congenital heart diseases (CHD).

PROJECT TITLE: **Discovery of Genetic Causes for Human Congenital Malformations**

RAC # 2091 038

PRINCIPAL INVESTIGATOR: *Majid Al Fayyadh, MD*

PROJECT DESCRIPTION: The acute and chronic morbidity and mortality imposed by birth defects have substantial medical, emotional and socioeconomic challenges for patients, families, communities and society. In most affected children, the cause of the birth defects, which are a leading cause of infant death, is unknown. To enrich the potential discovery of mutant alleles (especially recessive ones) causing congenital cardiovascular malformations (CCM), the aim of this research is to study these birth defects in Saudi Arabia where ~50% of marriages are consanguineous. This collaborative work brings together human molecular geneticists and clinicians to discover genetic causes of CCM.

PROGRESS: Ongoing.

PROJECT TITLE: **Protecta™ Clinical Study**

RAC # 2091 045

PRINCIPAL INVESTIGATOR: *Bandar Al Ghamdi, MD*

PROJECT DESCRIPTION: The Protecta™ Clinical Study is a prospective, non-randomized, multi-center study to support market release of the Protecta devices and evaluate the device features in reducing inappropriate shock.

The aims are to:

1. Evaluate the impact of the Protecta features in reducing inappropriate shocks,
2. Study secondary objectives including Quality of Life, Health Care Utilization and reasons for inappropriate shocks.

PROGRESS: 24 patients are enrolled in the study. Follow-up is going on.

PROJECT TITLE: **Left Ventricular Size and Function After Surgery for Severe Aortic or Mitral Valve Regurgitation at the KFHI: Long-Term Echocardiographic Follow-Up**

RAC # 2091 069

PRINCIPAL INVESTIGATOR: *Bjornstad Knut, MD*

PROJECT DESCRIPTION: The primary aim of this Study was to review the echocardiographic data on patients at the KFSH&RC who underwent surgery for severe aortic or mitral valve regurgitation from 1990 to 2005 and report on long-term outcomes of Left Ventricular size and systolic function.

PROGRESS: The Final Report was approved. 559 patients were enrolled and results showed a significant

reduction in mean left ventricular end-diastolic and end-systolic size after 1 year follow-up and at every postoperative interval until last follow-up (mean follow-up of 151 months), compared with preoperative size.

Post-operative end-diastolic and end-systolic size reduction was independent of which of the 5 alternative surgical procedures were chosen.

52 patients (29%) of the population needed at least one reoperation during follow-up.

Post-operative end-diastolic size reduction was independent of whether the patient needed reoperation during follow-up.

Mean fractional shortening was insignificantly lower in the group of patients who underwent reoperation during follow-up.

PROJECT TITLE: **Clinical & Molecular Characterization of Patients with Inherited Arrhythmogenic Disorders**

RAC # 2050 035

PRINCIPAL INVESTIGATOR: *Majid Al Fayyadh, MD*

PROJECT DESCRIPTION: This is a prospective study to identify genes responsible for inherited arrhythmogenic disorders in Saudi population. Consequently, detecting the causative mutations in affected families will serve several clinical purposes. This will enable clinicians to confirm the diagnosis, stratify patients, and apply prophylactic measures. Due to the fact that inherited arrhythmogenic disorders are characterized by incomplete penetrance, the most important contribution of mutation detection to patient management is the identification of asymptomatic carriers and hence, implementing prophylactic management.

PROGRESS: Ongoing. 63 families have been enrolled.

PUBLICATIONS AND INTERNATIONAL PRESENTATIONS

Abstract/Oral Presentations

- Z Halees. The Mini-Ross – Konno Procedure, *European Journal of Cardio-thoracic Surgery*. January 2011.
- Z Halees. An Additional Maneuver to Repair Mitral Paravalvular Leak. *European Journal of Cardio-thoracic Surgery*. February 2011.
- B Soufi, C Manlhiot, A Awan, M Ahmadi, A Omrani, B.W. McCrindle, A Wadei, Z Halees. Spectrum And Outcome Of Reoperations After The Ross Procedure In Children. June 2011.
- Z Halees , B Soufi, B Fadel, M Shahid, M Ahmadi, M Amri, Z Bulbul, A Omrani Current Outcomes Of The Glenn Bidirectional Cavopulmonary Connection For Single Ventricle Palliation. STS 48th Annual meeting, Florida. January 2011.
- B Soufi, C Manlhiot, A Awan, M Ahmadi, A Omrani, B.W. McCrindle, A Wadei, Z Halees. 20 Year Single Institution Expeience with Ross procedure. December 2011.
- Z N. Al-Hassnan, S Tulbah, A Hakami, A Al-Omrani, A Almesned, M Al-Fayyadh. SNP-based genome-wide analysis identifies a novel EFEMP2 mutation in four unrelated families with dilatation of the aortic root and ascending aorta. Abstract at the 12th International Congress of Human Genetics Montreal, October 11-15, 2011.

MEDICINE

SECTION OF ENDOCRINOLOGY

ENDOCRINOLOGY

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MEMBERS
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Abdulrahman Alnuaim, MD
Muhammad Hammami, MD
Ali Alzahrani, MD
Hussein Raef, MD
Nora Alkahtani, MD
Mohammed Almehthel, MD

These approved projects were presented at the European Neuroendocrine Meeting in March 2012 and also at the Endocrine Society Meetings in June 2012.

RESEARCH PROJECTS

PROJECT TITLE: **Atypical Pituitary Tumors: Incidence & Clinical Characteristics**

RAC # 2121-0160

INVESTIGATORS: *Mohammed Ahmed, MD, Hindi Al-Hindi, MD, Imaduddin Kanaan, MD*

PROJECT DESCRIPTION: Pituitary tumors are heterogeneous in proliferation rate, invasiveness, & recurrence. The prediction of tumor behavior & response to treatment has led an interest in an assessment of proliferative potential of the tumors. Ki-67(Ki) & p53 are indicators of aggressive behavior in WHO classification of Endocrine tumors.

PROLIFERATIVE INDICES: Ki-67 antigen is a protein related to cell proliferation and is expressed in cell nuclei throughout the cell cycle. P53 immunoreactivity represents expression of p53 gene product whose IHCS has served as an unfavorable prognostic marker. The relationship between Ki & p 53 labeling indices, pituitary tumor growth, invasiveness & recurrence is not settled. The 2004 WHO classification of pituitary adenomas includes an "atypical" variant defined as those with Ki-67 index of >3%, excess p53 immunoreactivity, & increased mitotic activity.

AIMS: To define the incidence clinical features & outcome of treated atypical pituitary adenomas.

MATERIALS AND METHODS: 154 consecutive cases of pituitary tumors operated between Jan 2006 & Jan 2012; 21 (CC) were categorized as atypical (per 2004 WHO classification). There were 11 males, 10 females, with median age 47, range 14-66 yrs. Tumor Types: These consisted of 8 prolactinomas, 5 GH-secreting, 5 ACTH-secreting, 3 clinically silent tumors. All prolactinoma pts. were resistant to dopamine agonist Rx. Visual Abnormalities: At Presentation (n=14) : 4 pts. were blind, 2 more had severe visual deterioration, 3 had optic atrophy, 3 had temporal hemianopsia, 2 had papilledema.

TUMOR CHARACTERISTIC: Size: median 41mm, range 14–56 mm long axis, all had suprasellar extension with chiasmal compression in 7, 8 had parasellar extension w/ encasement of carotid artery, 2 had 3rd/ lateral ventricles/hypothalamic compression, 2 had prepontine extension.

Treatment modalities:

Number of Surgeries	Number of patients
1	11
2	6
3	2
4	2

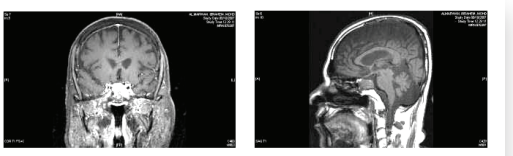
- 4 received XRT

RESULTS: Proliferative Indices: Ki median 5 %, range 3–95%, p53 immunoreactivity done in 16;10 +ve, median 5% range 1–100%.

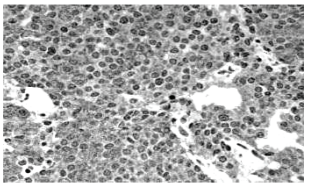
ACTH-PRODUCING PITUITARY MACROADENOMA

- Cushing's disease due to ACTH-producing pituitary macroadenoma is rare with a reported prevalence of 4–10%.

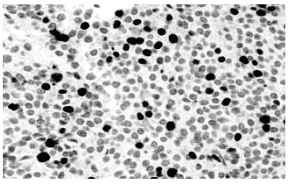
ACTH-Secreting Macroadenoma 2.5 cm Lesion



ACTH Immunostaining Stain Strongly Positive



Invasive ACTH-secreting adenoma, Basal ACTH left/right: 4095/764 ng/l, ratio 5.35 w/ high proliferative index:Ki-67 (8%)



ACTH-PRODUCING CARCINOMA: One patient with ACTH-secreting adenoma with initial Ki <3% & -ve p53. Recurred as an atypical adenoma with Ki-67 index of 10 % and p53 +ve 1%. Ultimately progressed to carcinoma with metastases to L4 vertebra, and rt. 4th rib with each of these indices of >80 %.

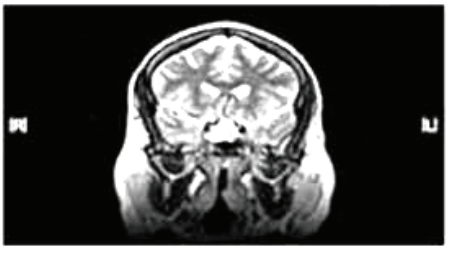


Figure 1. MRI (coronal view) Post First TSS, these are two components of pituitary tumor coalescing together with central necrosis. The lesion measures 22 x 17 x 19 mm. Note: extension to the right cavernous sinus suprasellar extension. The cavernous portion of the right internal carotid artery is partially encased by the lesion.

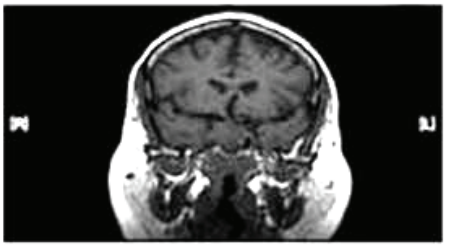


Figure 2. MRI (coronal view) Pituitary tumor operated twice in the past. The patient still has residual tumor. Note: heterogeneous right pituitary lesion that measures 27 mm x 19 mm. There is suprasellar extension of the tumor with no significant compression on the optic chiasm.

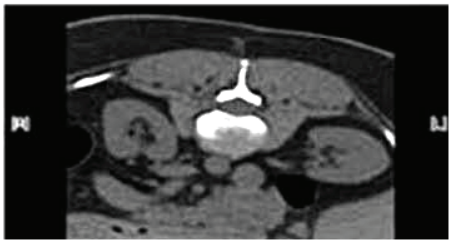


Figure 3. CT: L4 vertebral body shows sclerotic lesion.

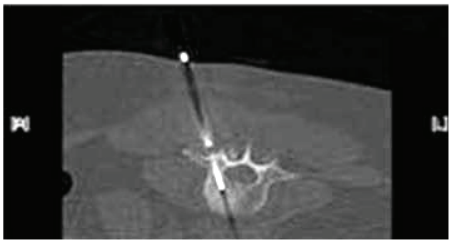


Figure 4. CT-guided Bx of L4 vertebral pedicle showed metastatic carcinoma compatible with pituitary origin.

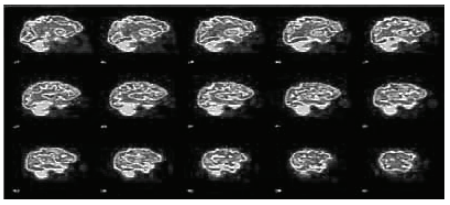


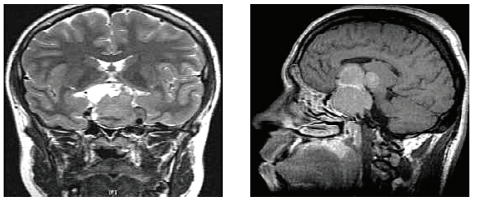
Figure 5. FDG PET-CT Brain shows an intensely hypermetabolic lesion in the region of the sella/surasellar location with maximum SUV of 16 suggestive of high proliferative index.

Sequetial changes in immunohistochemical markers indicating evolution of pituitary adinoma into carcinoma

Immuno Markers	2003	2006	2007
Synaptophysin	++	++	+++*
Chromogranin	ND	+	+*
ACTH	++	+	+FAINT (F)
GH	-	+F	-
PRL	-	-	-
AE1/AE3	++	+++	+++*
CAM5.5	+++	+++	+*
CKZ	-	-	++*
CK20	-	-	R*
CK19	ND	+F	+++*
EMA	-	-	+*
Vimentin	ND	-	+++*
CEA (BG++)	-	+F	+++*
CD15	++	+++	+F*
TTF-1	-	-	++*
MIB-1	<3%	5-10%	>20%
p53	0	<1%	100%

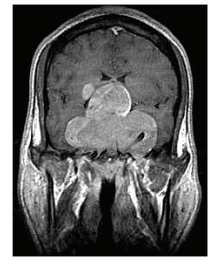
INVASIVE PROLACTINOMA

- 14 yr. old male Prolactinoma, Prl 7227ug/l. Sellar/suprasellar complex, partially cystic mass with heterogeneous enhancement of solid component. Ki-67 12% P53 negative, consistent with a pituitary macroadenoma. It measures about 4 cm in maximum dimension. The chiasma is pushed superiorly and anteriorly by the lesion.



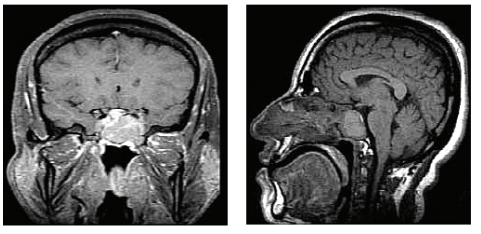
INVASIVE GH-SECRETING ADENOMA

- 22 Y Male, GH Tumor, Large lobulated, heterogenous sellar mass measures (AP x T x CC = 56 x 81 x 59 mm) with multiple areas of cystic and hemorrhagic degeneration. Significant compression to the optic chiasm and encasing the bilateral ICA with cavernous sinus effacement. And extending anteriorly to the sphenoid sinus and ethmoidal sinuses. Chiasmal compression, surgery x 2, KI 10% P53 pos.



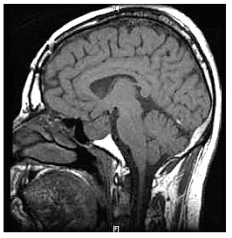
GH-SECRETING TUMOR

- Histology: "atypical tumor", Ki-67 index 3%, P53 10%.



CLINICALLY SILENT TUMOR

- 50 yr. old male left suprasellar component distorted optic chiasm. Lateral displacement of the cavernous sinuses. Erosion of the tuberculum sella and dorsum sella. Ki 67 index 5%.



FOLLOW UP: Follow up period median 37 months, range 1-144. Tumors persisted (12), progressed (4), recurred (3), remitted (1) patient, one w/ carcinoma is dead.

CONCLUSIONS: Incidence of atypical pituitary tumors was 13.6%. These were characterized as invasive tumors. Associated with visual defects in 67%. Associated with tumor persistence/recurrence/progression (20/21; 95%), requiring aggressive surgery with poor outcome. A high proliferation rate is associated with progression of an atypical adenoma to carcinoma in one ACTH-secreting tumor. Prolactinomas resistance to medical Rx indicate invasive behavior with a high proliferation index necessitating surgery without further delay.

PROJECT TITLE: **Dysgenetic Male Pseudohermophrodite: Impact On Gender Identity Along With Clinical Features And Management**

RAC # 2120-032

INVESTIGATORS: *Mohammed Ahmed, MD, Abdulrahman Alnuaim, MD*

PROJECT DESCRIPTION

INTRODUCTION: Male Pseudohermaphrodite (MPH) is defined as an individual whose genital differentiation is not that expected of normal male, despite 46, XY and presence of testes. Differential Dx include: defect in androgen action, defects in testicular activity such as 17-KS reductase deficiency, Leydig cell agenesis/hypoplasia, or testes regression syndrome.

AIMS: To define diagnostic and management considerations for dysgenetic (MPH) due to defect in testicular activity and its impact on gender identity.

CASE SUMMARY: A 19-year old medical student raised as a female sought medical advice for amenorrhea, and acne.

PHYSICAL EXAMINATION: revealed ambiguous external genitailia, bilateral inguinal gonads, clitoromegaly, blind-ending vagina. Karyotype: 46, XY.

HORMONAL EVALUATION: Serum testosterone (T) 1.79 nml/l (RR: male 9.9-27.8) Dihydrotestosterone (DHT) 0.19nmo/l(RR: 0.1- 0.8). Following 4 days HCG stimulation; T increased 4.14, & DHT increased 0.4, Androstenedione: 3.3 nmol/l; (RR: 1.0-12.2), DHEAS: 5.29 nmol/l (1.8-8.3), 17-OH-Progesterone 2.0 (RR: 0.3-3.3), LH: 30.7 IU/l (RR: 1.7-8.6), E2: 32 pmol/l (RR: male 28-156 & female 46-774), FSH:48 IU/l (RR: 1.5-12.4).

UROLOGY EVALUATION: under general anesthesia revealed: a 3 cm phallus, Cystoscopy findings: long male-like urethra, Vaginoscopy: blind-end 1.5 cm vagina.

LAPROSCOPY FINDINGS: Wolffian duct derivatives (spermatic cords, atrophic testes, epididymis and Vas deferens) were identified, as evidence for fetal testicular testosterone production/action. There was absence of uterus, tubes and ovaries, attesting to AMH generation/action from fetal sertoli cells during gestation. Above stated findings were not in keeping with 5 alpha-reductase deficiency nor 17-Ketosteroid reductase deficiency. Possibilities for this male pseudohermaphrodite included Leydig cell agenesis/hypoplasia, or testes regression syndrome. The Dx of leydig cell agenesis for this patient is based on little or no increase in testosterone to HCG/LH, mullerian regression is complete because secretion of AMH by sertoli cells is not impaired. Patient was seen by 3 mental health experts rendering the opinion that Patient and the family are welladjusted with established female identity, with female sexual and social adjustment. Patient did not wish to change sexual

identity, and wanted orchidectomy. Bilateral orchidectomy was done, and patient remains satisfied.

TESTICULAR HISTOLOGY: Sertoli-cell only with no evidence for testicular tumor.

CONCLUSION: Male Pseudohermaphrodite with ambiguous external genetalia develop female gender identity and should be raised as females, with gonadectomy performed because of high risk of gonadoblastoma in dygenetic undesended testes.

PROJECT TITLE: **Factitious Hypoglycemia: A Manifestation Of Youngter's Bullying**

RAC # 2120-037

INVESTIGATORS: *Mohammed Ahmed, MD, Talal Al Otaibi, MD, Abdulelah Al-Mutairdi, MD*

PROJECT DESCRIPTION

INTRODUCTION: The greatest source of (youngster) stress is the one some inflicts on others: bullying; defined as an act by an overbearing person who habitually badgers and intimidates smaller or weaker people. Bullying can result in social maladjustment with grave consequences. We report 2 young ladies ages 15 (pt. A) and 19 years (pt. B) who took recourse to covert ingestion of glyburide resulting in near fatal effects in one. In Pt. A it resulted in unwarranted investigations, expense, a loss of one year of schooling, a delay in Dx and management at an outside facility. A correct Dx was arrived by documentation of insulin (IN) and proinsulin (PRO) to C-peptide (CP) ratio <1 with concurrent hypoglycemia and circulating Glyuride. Both were provided with parental and psychological support.

Factitious hypoglycemia (FH) occurs from surreptitious use of insulin/secretogogues (sulphanylurea/meglitinides).

Biochemical/hormonal findings may be indistinguishable form insulinoma. It is probably more common than realized, especially among younger individuals with social maladaptation. The challenge in the Dx of factitious hypoglycemia can be surmounted in part by determination of molar ratio of insulin to C-peptide; these are secreted in the portal circulation in a equimolar (1:1) ratio.

Under physiological conditions a large fraction of endogenous insulin is cleared by the liver in the first pass, whereas C-peptide passes thru the liver with essentially no extraction. An insulin/Cpeptide ratio CPR >1 during hypoglycemia argues in favor of surreptitious insulin use. Whereas an insulin/C-peptide ratio <1 should be the case for sulfonylurea use or insulinoma, along with serum detection of sulfonylurea providing the distinction between the two.

AIMS: To define factors predictive of factitious hypoglycemia.

CLINICAL CASES: We present two young ladies ages 15 (Pt. A) and 19 years (Pt. B) who presented with impressive recurrent profound hypoglycemia, fulfilling Whipple's triad. They covertly used glyburide in the background of social maladjustment.

PATIENT A: Aged 15 years, had a 2-year history of severe neuroglycopenic symptoms, intermittent loss of consciousness, seizures, initially misdiagnosed as epilepsy, and she was intubated for 4 days at an outside hospital. An extensive evaluation done outside included: documented hypoglycemia (2 mmol/l), hyperinsulinemia, and high C-peptide. Other test done at the outside facility: insulin antibodies, insulin receptor antibodies, total body CT/MRI, EEG, yielded negative results. She continued to receive 6 meals/day with fairly constant dextrose 10-25% infusions thru an in-dwelling central venous catheter upon exhaustion of all peripheral venous access that resulted in catheter infection and systemic sepsis requiring admission to ICU again at the outside facility for a month long admission. Finally she was transferred under our care with a tentative Dx of insulinoma. Our lab findings: within 2-hrs. of fast following results unfolded: hypoglycemia (2 mmol/l), hyperinsulinemia (insulin 137 pmol/l; RR: 17.8-173), hi C-peptide(0.98 nmol/l;RR: 0.38-0.65), hi proinsulin (32 pmol/l;RR:3-20), with insulin/C-

peptide ratio: 0.14, proinsulin/Cpeptide ratio: 0.03, positive serum toxicology for glyburide using liquid chromatography tandem mass spectrometry (LC/MS/MS). The parents of the pt. were "shocked" with this revelation.

Initially patient denied vehemently but with discrete persuasion admitted surreptitious use of glyburide. Psychological support led her to reveal peer pressure in using the drug and had used 36 labs (180 mg) glyburide on the day of her outside ICU admission.

Although she had been absent from the school for a year related to her health problem, she had been in contact with a "friend" at school who had established a network providing the drug to her and several other girls. Peer acceptance was the major reason for the drug abuse. The social and Psychiatric services were involved in contacting parents and school authorities for corrective measures.

PATIENT B: University student had a history of weight gain (had used Xanical for weight reduction), neuroglycopenic symptoms, 12-hr obtundation and documented recurrent hypoglycemia (bold glucose 36 mg/dl) at her local hospital wherein she was hospitalized for 21 days with IV glucose support. She signed out against medical advice only to be readmitted to the same local hospital with recurrent hypoglycemia. Our evaluation: Within 6 hrs of fast following lab results enfolded: blood glucose 2.1 mmol/l, serum insulin 403 pmol/l, C-peptide 3.31 nmol/l, proinsulin 30, Insuiln/C-peptide ratio 0.12, Proinsulin /C-peptide ratio 0.015, serum positive for glyburide but negative for meglitinides. Upon informing the issue, patient admitted to social conflict and rejection by a life-long girlfriend, leading to depression that pushed her to consume her father's prescribed supply of glyburide. Patient was provided with parental and psychological support.

CONCLUSIONS: The possibility of factitious hypoglycemia must be always entertained in the evaluation of hypoglycemia. It is probably more common than realized, especially among younger individuals with social maladaptation. The challenge in Dx of factitious hypoglycemia can be surmounted in part by determination of molar ration of insulin to C-peptide with serum drug detection being most definitive in arriving at the correct Dx. Factors predictive of this possibility include: a younger age, social stress, adjustment disorder, bullying, peer pressure setting, and atypical chaotic occurrence without relation to fasting or meals. The dx can be established by documentation of concurrent hypoglycemia, hyperinsulinemia, hi Cpeptide/ proinsulin, the molar ratio of insulin and proinsulin to Cpeptide <1 and detection of serum insulin scre-togogue in the same sample.

PROJECT TITLE: **Cortisol, Estradiol (E2) And Anrdogen-Secreting Adrenal Cortical Carcinoma (ACC)**

RAC # 2110-200

INVESTIGATOR: *Mohammed Ahmed, MD*

PROJECT DESCRIPTION

BACKGROUND: We report a case of adrenal cortical carcinoma (ACC) associated with high levels of serum cortisol (CS), testosterone and estradiol (E2). Although not studied specifically in our case, nevertheless, it provides a model for understanding sex-steroid metabolism in ACC. Elevated E2 in patients with ACC is due to probable dual source of E2 from tumor and peripheral conversion of tumor-derived androgens (1). Aromatase is the terminal enzyme responsible for E2 biosyntehesis. High levels of aromatase protein and mRNA have been demonstrated in ACC but not in adjacent normal tissue (2). Aromatse gene (C19) is regulated in cell-specific manner via alternative use of various promoters in first exon (3).

Promoter II mainly directs expression of armoatase gene in all testicular cell types (3). Androgens upregulate aromatse gene expression in purified adult germ cells (4). The case suggests that utilization of promoter II-directed gonadal-type exon 1 might be involved in over production of aromatase in E2-secreting ACC.

CLINICAL CASE: A 27-year old man presented with Cushing's syndrome (CS) and gynecomastia.

HORMONAL EVALUATION: Consistent with ACTH-independent CS : elevated 24-hr urinary free cortisol (UFC:3388 nmol, nl,<250), AM serum cortisol:1312 nmol/l, (nl, <220), ACTH< 1 ng/l,(nl 5-60), E2x2: 45,950 and 44, 613 pmol/l, (nl 28-156), testosterone >26 nmol/l x3, (nl,9.9-26), androstenedione >70 nmol/lx3 (nl,2.4-12.6), 17-OH-PX2: 2090 and 2650ng/dl,(nl,55-455) DHEAS280 ng/ml (nl,<13).

IMAGING STUDIES: CT/MRI/FDG-PETCT showed 11x10 cm right adrenal tumor with liver, and IVC invasion, total occlusion of IVC extending cranially within 3 cm right atrium (figure 6–9), and lung metastases. FU images: Extensive necrosis with a coincidental drop in E2 to 8,251, UFC to 67 and serum cortisol to 339, ACTH increased to 31, all these unrelated to laprotomy for unresectable ACC followed by re-surgence of hypercortisolemia (UFC 2297, Serum cortisol 1231, Drop in ACTH <1). These findings are illustrated in figures 5 and 6.

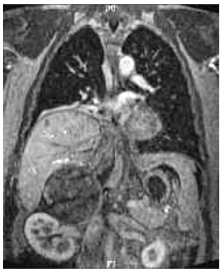


Figure 6. Multiplanar, multisequential MR images of the abdomen showing a bulky mass lesion in the right suprarenal region measuring about 11.7 x 9.1 x 10.9 cm. displacing right kidney downwards and laterally.

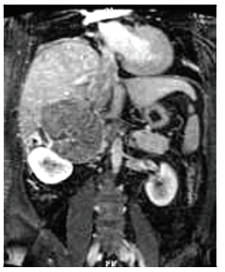


Figure 7. MR images of the abdomen: Note capsular discontinuity adjacent to the Intrahepatic portion of the IVC (arrow) with tumoral extension cranially in the IVC about 8.5 cm. The upper portion of the abdominal IVC demonstrates nonenhanced thrombus of about 4.5 cm in craniocaudal dimension. The right kidney is partly displaced inferiorly by the mass lesion which abuts the superior/medial aspect of the kidney with no definite invasion.

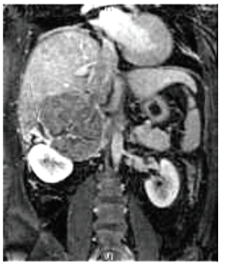


Figure 8. MR images of the abdomen: Note an area of capsular dis continuity adjacent to the hepatic segment # 6 (arrow) with tumoral extension to the adjacent hepatic parenchyma.

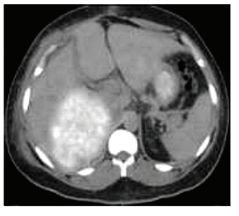


Figure 9. PET Scan demonstrating avid uptake of FDG by the right adrenal carcinoma.

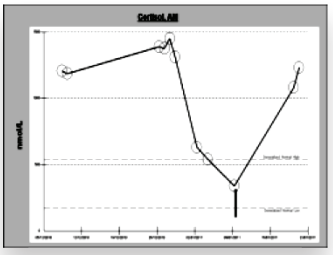


Figure 10. Extensive spontaneous tumor necrosis with a drop in serum cortisol to 339 nmol/l (arrow), increased ACTH (31 ng/l:not shown), with a coincidental drop in E2 to 8,251 pmol/l (not shown): all these were unrelated to laprotomy for unresectable ACC followed by resurgence of hypercortisolemia (Serum cortisol 1231, and a drop in ACTH <1).

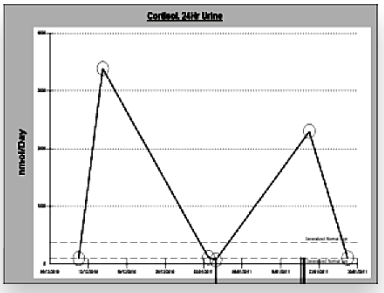


Figure 11. Extensive necrosis with a drop in urine free cortisol (UFC to 67 nmol/l: single arrow) , coincidental increased ACTH to 31 ng/l (not shown): followed by resurgence of hypercortisoluria (double arrow: UFC 2297 nmol/l), and a Drop in ACTH <1 (not shown).

HISTOPATHOLOGY

Compatible with ACC with high nuclear grade, extensive hemorrhage and necrosis. Immunostains: positive for cal-retnin, I nhibin, melan A, AE1/AE3, CAM 5.2.

TREATMENT

Mitotane, ketoconazole, and Metyrapone tried without response. Patient considered not a candidate for Chemo/Radiation therapy.

CONCLUSIONS

The case supports the notion that E2-secreting tumors in adult males are frequently carcinomas. Extensive tumor necrosis can result in cyclical steroid hormonal changes. The case provides clinical model for understanding of sex-steroid metabolism in ACC, lending support to the concept that high androgenic production by tumor leads to excess E2 synthesis by up-regulating Aromatse gene (C19).

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PROJECT TITLE: **Prenatal Androgen Exposure Imprinting Establishes Gender Identity**

RAC # 2120 034

INVESTIGATOR: *Mohammed Ahmed, MD, Abdulraof Almahfouz, MD, Abdulrahman Alnuaim, MD*

PROJECT DESCRIPTION

BACKGROUND: The underpinning of gender identity is a complex interplay of genetic, hormonal, neuronal and social expectations. It has been difficult to dissect the importance of genetic versus hormonal impact on gender identity. Controversy prevails

whether prenatal androgen exposure predict gender identity or not.

AIM: We report a case of Congenital Adrenal Hyperplasia with 46, XX karyotype presenting in adult life with complete vi-rilization and established male identity. Findings here indicate gender identity may be engraved in brain early in life, regardless of genetic compliment & how puberty unfolds.

CASE SUMMARY: An 18-year old person with ambiguous genetalia was initially raised as a female. However, at pubertal age amenorrhea, lack of breast development, excess body hair, were noted. By this time there was well established male sexual identity with necessary legal work completed by the patient and his family. Patient was lost to FU till age 27 years when the person presented to Urology for reconstructive genital surgery and was referred to Endocrine service.

PHYSICAL EXAMINATION: Revealed a Phenotypic male, muscular, fully breasted beard, mustache, and thick body hair, short statured (height: 145 cm), worked as male clerk . The patient had ambiguous external genetalia, prominent labial folds, 5 cm clitoromagaly, with redundant foreskin, corona, and urogenital sinus with 5 cm long vagina.

IMAGE FINDINGS: Genitogram: cervix , hypoplastic uterus, tubes and vagina were identified. US/CT Pelvis: hypoplastic uterus, thin endometrium, Cervix, rudimentary ovaries and tubes. CT Abdomen: Symmetrically enlarged adrenal glands. Karyotype Findings: 46, XX

HORMONAL EVALUATION: Baseline values 17-OH-Progesterone: 538nmol/l(nl<6.7), 17-OH-Prgenenalone: 278 ng/dl (nl, 53-357), cortisol 202nmol/l (RR:170-536), Post Synacthen stimulation values 649/4550/371 respectively. Serum ACTH 138 ng/l (nl, 5- 60). Serum testosterone 20.19 nmol/l (nl, male 9.9-27.8), DHEAS 18.65 umol/l (nl, 4.2-11.5), E2 149 pmol/l (nl, 46-774), FSH 0.8/LH <0.1 IU/l. patient insisted on corrective surgery.

MANAGEMENT PLANS: Psychological Support, Surgery planned for augmentation phaloplasty, hysterectomy, vaginoplasty with UG sinus to continue as voiding source.

CONCLUSIONS: Prenatal androgen exposure in a genetic female predicts male gender identity. Patients with CAH and complete virilization have high risk of being diagnosed late in life. For 46, XX patients with established male gender identity it is appropriate to augment male gender identity, undertake hysterectomy/oopherectomy, as has been practiced in different cultures in Middle East & West.

PROJECT TITLE: **Long-Term Survival In A Patient With A Large Adrenal Cortical Carcinoma Producing Cortisol And Androgens**

RAC # 2120 033

INVESTIGATORS: *Mohammed Ahmed, MD, Rashid Al Muqbali, MD*

PROJECT DESCRIPTION

BACKGROUND: Adrenal Cortical Carcinoma (ACC) is a rare endocrine malignancy with an estimated worldwide incidence of 0.5-2 per million/year. It is characterized by a high risk of recurrence; even after radical surgery up to 85% patients develop recurrence. A decreased overall survival around 30 % is reported in most series. Tumors localized to adrenal gland (McFarlane stages 1 and 2) have a better prognosis than invasive & metastatic tumors (stages 3 and 4). Important factors dictating outcome include, patients age, tumor stage, resection status at initial surgery, overexpression of molecular markers such as IGF-2, constitutive activation of beta-catenin and adjuvant therapy administered.

Whether the use of mitotane is beneficial as an adjunct Rx remains controversial. Patients with high-stage tumors were reported to have demonstrated clear survival advantage with mitotane serum levels above a threshold of 14 mg/l. Long-term survival of a decade or more is limited to few cases. Little information is available regarding survival status

of patients with ACC produc-ing both cortisol & andogens.

AIM: To define factors favoring long-term disease-free survival in multihormone-producing adrenal carcinoma.

CASE SUMMARY: A 21-year old lady with amenorrhea, and with amenorrhea, and hirsutism presented to us in 2000. O/E she had acne, hirsutism (Ferriman-Gallawey score 3), with prominent features of Cushing's syndrome. Lab Investigations: Serum AM/PM cortisol (776/856 nmol/l: nl:-170-356/125 -220) showed loss of diurnal variation, Urine free cortisol 604 nml/d (nl: <220), Serum ACTH < 10 ng/l (nl:5-60), testosterone 16 nmol/l (nl, female: 46-774), DHEAS 53.6 umol/l (nl 2.2-15.2). CT abdomen/Chest/Pelvis: 12.5x 10.5 cm left adrenal mass, without evidence of regional or distant metastases. She underwent laparoscopic complete resection. Histology: findings compatible with ACC 19x11x 9 cm, weighing 643 grams, with focal capsular invasion but without extracapsular extension. Adjuvant mitotane Rx was started and is continued to date in a dose of 1G TID, along with prednisone 5 mg daily. Serum mitotane monitoring has not been available. Aside from mitotane She has not received any other treatment.

FOLLOW UP COURSE: For the last 11 years she has been under surveillance using Q 6-12 monthly using CT, US abdomen, liver function tests, serum & urinary cortisol, androgens; these and all other laboratory parameters have remained unremarkable with no evidence of recurrence or metastases, nor any side effects of mitotane Rx. She is fully functional as a teacher chose to become became pregnant x3 during which she withheld mitotane for a cumulative duration of 30 months. She lost one pregnancy but the 2 other pregnancies were normal and is raising 2 healthy children.

CONCLUSIONS: Favorable factors for disease-free survival in our pt. included young age, McFarlane low-stage tumor, complete resection, lack of metastases, and possibly use of mitotane.

Adjunct mitotane may prolong recurrence-free survival in patients with radically resected ACC producing cortisol and androgens. Mitotane should be considered in most ACC patients.

PROJECT TITLE: **Challenges In The Management Of A Large Disseminated Malignant Abdominal Paraganglioma**

RAC # 2110 181

INVESTIGATORS: *Mohammed Ahmed, MD, Tarek Amin, MD, Shouki, Bazarbashi, MD, Hindi Al-Hindi, MD*

PROJECT DESCRIPTION

BACKGROUND: Paragangliomas (PGLs) are rare neuroendocrine tumors that arise from hyperplastic paraganglionic cells and occur in or near the ganglia of the autonomic nervous system (1). PGLs can be either functional or nonfunctional based on production of neurotransmitters (1). The sympathetic-associated PGLs are usually functional and often arise in the abdomen (2). Pheochromocytoma-PGL syndrome is frequently hereditary condition and is caused by germline muta-tions in the SDHB, SDHC, or SDHC genes.

SDH mutations induce angiogenesis and tumorogenesis through the inhibition of hypoxia-inducible factors (HIF)-propyl hyroxylase. Most abdominal and thoracic PGLs associated with succinate dehydrogenase (SDHX) mutations hypersecrete catecholamines and dopamine (3). However, 10% tumors are biochemically silent (4). SDHX B, C, and D mutation associated PGLs manifest as rather distinct clinical phenotypes. Germline mutations of genes coding for succinate dehydrogenase subunits B (SDHB) and D (SDHD) predispose to paraganglioma syndrome type 4 and type 1 respectively (5).

AIM: To correlate the genotype-phenotype relationship in a patient with SDHX B mutation associated voluminous abdomino-pelvic non-functioning malignant PGL.

CASE SUMMARY: Herein we describe the clinical, hormonal, imaging, histopathological, genetic

analysis, therapeutic and follow up data of a patient with a large abdomino-pelvic non-functioning PGL. Therapeutic measures involved repeated pre-operative embolisation of hypervascular PGL aimed to reduce tumor vascularity, followed by a combination of extensive near total excision and intraoperative radiofrequency-electro ablation of the tumor that preceded use of octrotide LA, I-131 MIBG, and chemotherapy in sequence.

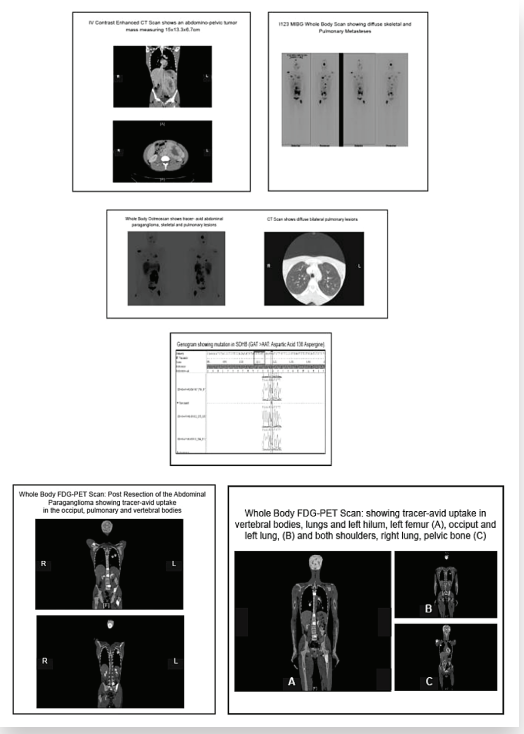
MATERIALS AND METHODS: A 20-year old single male, was referred with a 3-year history of a large skull occipital mass, a large abdominal incidentaloma, had a core biopsy of the abdominal mass done at the outside hospital with a diagnosis of paraganglioma. Under our observation patient had frequent round the clock blood pressure monitoring for 8 weeks. Imaging studies consisted of CT scans of abdomen, chest and pelvis, CT head and neck, 1-123 MIBG scan, Octreoscan, whole body PET and whole body bone scan, skeletal survey, and abdominal angiogram in preparation for repeated preoperative tu-mor embolization. Following hormonal and biochemical studies were done: 24-h urinary metanephrine and normetanephrine determinations x3, urinary epinephrine, norepinephribe, dopamine, serum free catecholamies, and dopamine, chromogranin A (CGA), calcitonin, CEA antigen, CBC, liver and kidney function tests. Molecular genetic stud-ies for mutations in SHDB, SHDC and SDHD, VHL, RET were also carried out.

RESULTS: Our review of outside core biopsy revealed uniform polygonal cells showing strong staining for CGA, synaptophysin, and S-100 protein; findings consistent with paraganglioma. Blood pressure readings showed an occasional systolic peak of 140 and a rare diastolic peak of 90 mm Hg and no symptoms attributable to catecholamine excess. Imaging studies revealed a large lobulated intensely enhancing thick walled, abdomino-pelvic tumor mass measuring 15x13.3x6.7cm with central necrosis, bilateral pulmonary lesions , multiple disseminated skeletal lesions (involving skull with intracranial extension, both humerii, left scapula, right third rib, manubrium sternii, left mandible, several vertebral bodies of T4, T12, L2 , and L5 with expansile destructive lesion extending intraspinally, displacing the spinal cord, and compromising neural foramina, with additional lesions in sacrum, iliac and pubic bones. The primary tumor and majority of the metastatic lesions showed avid uptake of both MIBG, octreotide and 18-Fluro2-deoxy glucose tracers. However, the liver was free of lesions. Angiogram showed an exuberant vascular supply from multiple sources originating from aorta, celiac axis, superior and inferior mesenteric, lumbar, and left renal arteries. Serum and urinary catecholamines all were within normal limits with the exception of a single urinary normetanephrine value that was modestly increased to 4.78 umol/l (Ref. Range 0-3.43). Serum CGA was 3210 ng/ml (normal <225), Calcitonin 2.6 pmol/l (RR 0.1-5.5), CEA antigen 1.2 ug/L (RR: 0-3.4), hepatic and renal function tests were all within normal limits. Tumoral Ki-67 index was 1%. Patient had mutation in SDHB (GAT >AAT: Aspartic Acid 138 Aspergine). Genetic analysis for family members is pending.

CLINICAL COURSE: Repeated tumor embolization x3 was done preoperatively and patient underwent a combination of extensive resection, and radiofrequency-electro ablation of approximately 98% of the abdomen-pelvic tumor that was adherent to the abdominal aorta, inferior vena cava and the left ureter. For the metastatic disease patient received Octreotide LA Q monthly injections, and 1-131 MIBG (210 mCi) and Serum CGA declined to 7 ng/ml without an impact on the imag-ing-visualized tumor burden. Accordingly, chemo therapy (Temozolomide/ Capecitabine) was started. Three months later, CT findings indicate mild interval regression of pulmonary lesions, stability of skeletal lesions with no new find-ings. Additional therapy may consist of an inhibitor of the mammalian target of rapamycin (mTOR) alone or in conjunction with peptide receptor radiotherapy (RRRT) using LU-177-DOTA-TATE.

CONCLUSIONS: The case defines following genotype-phenotype features of PGL syndrome type 4:

1. SDHB mutation predisposing to extradrenal PGLs, and a high malignant potential with symptoms related to tumor mass effect rather than to catecholamine excess.



2. An intensely hypervascularity tumor, and the need for repeated preoperative tumor embolization.
3. The value of radionucelide diagnositic scans for comprehensive localization of SDHB-PGL.

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PROJECT TITLE: **Primary Neuroendocrine Tumor of Parathyroid**

RAC # 2110 193

INVESTIGATOR: *Mohammed Ahmed, MD*

PROJECT DESCRIPTION

INTRODUCTION: Parathyroids are derived from the third and the fourth branchial pouches. The neuroendocrine C-cells originate from the fifth branchial pouch. A close ontogenic relation between these embryonal pouches and their derivatives is illustrated in DiGeorge syndrome wherein there is absence of parathyroid glands and the Ccells. It is not known for sure if normal parathyroids harbor neuroendocrine cells. However, neuroendocrine tumor (NET) of parathyroid has been reported in two previous cases (Medline Search: 1966-2011).

AIM: We report a third case of primary NET of parathyroid, along with the treatment given and follow up (FU) course. The case indicates presence of neuroendocrine cells in parathyroid and their potential to undergo tumoral transformation.

MATERIALS AND METHODS: A 61-yr. old lady presented to her local hospital with anterior neck mass, stridor and dyspnea. Investigations and treat-ment she received at outside included: CT scan showing right thyroid lobe mass; thyroidectomy was performed, and at surgery an 8 cm hard right neck mass, adherent to strap muscles, trachea and carotid sheath was found. The patient was referred to us.

Our review of histopathology intrathyroidal 8 cm, invasive parathyroid NET, with multiple vascular em-boli, and perithyroid extension with Ki67 index 5%. Immunostains: chromogranin+, synaptophysin & PTH weak +, thyroglobulin-, TTF1-, p53. (Figure 1).

FOLLOW UP COURSE: Dyspnea & stride got worse; US Neck showed multiple locally invasive soft tissue masses largest measuring 3.4 cm. CT scan of the neck and chest (Figure 2) mass lesion infiltrating right half of tracheal wall and exophytic tumor growth into the lumen of trachea, along with bilateral pulmonary metastases (Figure 3) and osteolytic vertebral metastases of C4 and C6 (not shown). PET-CT (Figure 4) showed avid uptake of FDG in peri/intratracheal tumor/ Cervical vertebra (C4) very close to cervical cord (Figure 5). Bone scan was negative. Repeated serum Ca++, PO4-, PTH, ALKptase, albumin thru January 2012 were normal.

MANAGEMENT: Consensus of multidisciplinary group: She was considered neither a suitable surgical candidate, nor for chemo therapy, nor for Gamma-knife, nor IMVT (hi dose fractionated Radiation), for fear of tracheal perforation. Stabilization of airway was considered to be of paramount importance. Bronchoscopic radio-fulguration of tracheal lesion resulted in complete relief of tracheal obstruction (Figure 5) and respiratory distress. External beam radiation was given for vertebral lesions. Patient is alive 3 years with progression of neck and lung lesions.

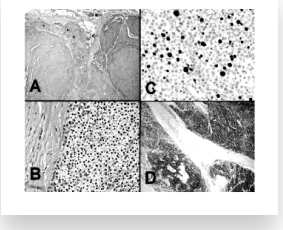


Figure 12. Photomicrograph of resected parathyroid showing neuroendocrine cells infiltrating into surrounding tissue; low power view (**A**), medium power view (**B**), tumoral Ki67 index 5% (**C**) and immunostaing positive for chromogranin (**D**).

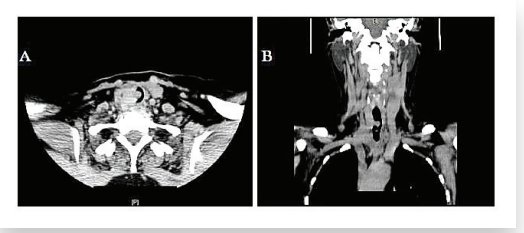


Figure 13. CT Images Neck: Coronal View (**A**) & Sag-ittal View (**B**) showing right neck tumor with intratracheal exophytic extension.

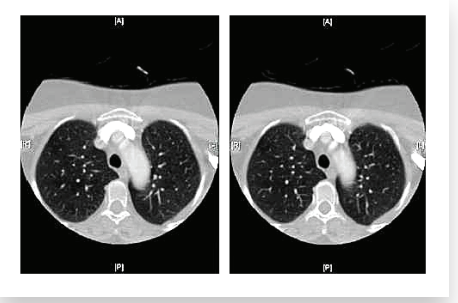


Figure 14. Pulmonary Nodules Progression.

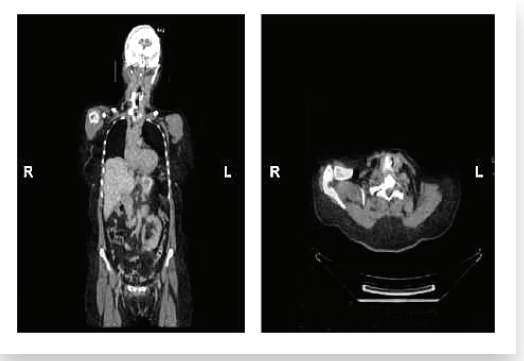


Figure 15. PET-CT showing intratraheal obstructive infiltration of the right neck tumor.

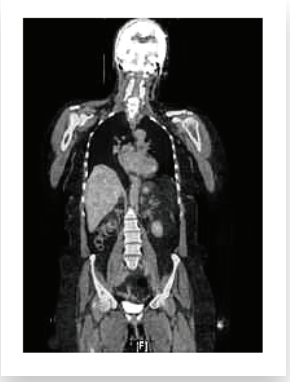


Figure 16. PET-CT showing vertebral metastasis.

CONCLUSIONS: Our case documents NET of parathyroid gland as a recognized, albeit a rare entity. It should be distinguished from parathyroid adenoma/carcinoma or metastatic to ensure proper management.

PROJECT TITLE: **Malignant Carotid Body Tumors (CBTs), Clinical Presentation, Investigations, And Their Management**

RAC # 2110 193

INVESTIGATORS: *Mohammed Ahmed, MD, Mamdouh Tuli, MD, Abdulaziz Al-Sugair, MD, Hindi Al-Hindi, MD*

PROJECT DESCRIPTION

INTRODUCTION: Carotid Body Tumors (CBTs) are tumors of neural crest origin that arise form chemoreceptors. They are usually benign, highly vascular, nonfunctional paragangliomas.

Paragangliomas are tumors that arise from extraadrenal chromaffin cells and originate from the parasympathetic or sympathetic ganglia. Head & neck paragangliomas are mostly derived from parasympathetic ganglia. The clinical course of carotid body paragangliomas is characterized by 2 modes: locoregional growth or malignant with distant metastases. Malignant CBTs are very rare (incidence 0.012%) and their management strategy is not well settled. We present 2 pts. with malignant CBTs to define their presentation, investigations done and treatment undertaken with a follow up (FU) course.

AIMS: To provide evidence that malignant CBTs can be managed meaningfully using surgical resection & multimodal therapy.

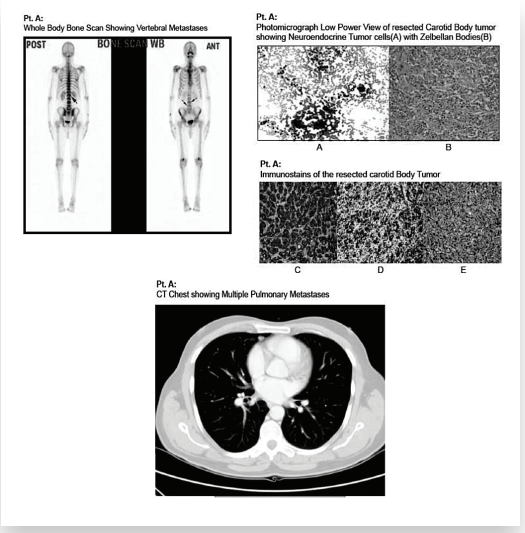
MATERIALS AND METHODS: Two patients with large (Shamblin class 3) CBTs were investigated using FNA followed by resection after tumor embolization. Immunostains were done for chromogranin A (CGA), synaptophysin, along with Ki-67 index. Imaging studied performed included US neck, CT neck/Chest, MRI, PET-CT, MIBG, bone and Octreoscans. Serial serum CGA were also done.

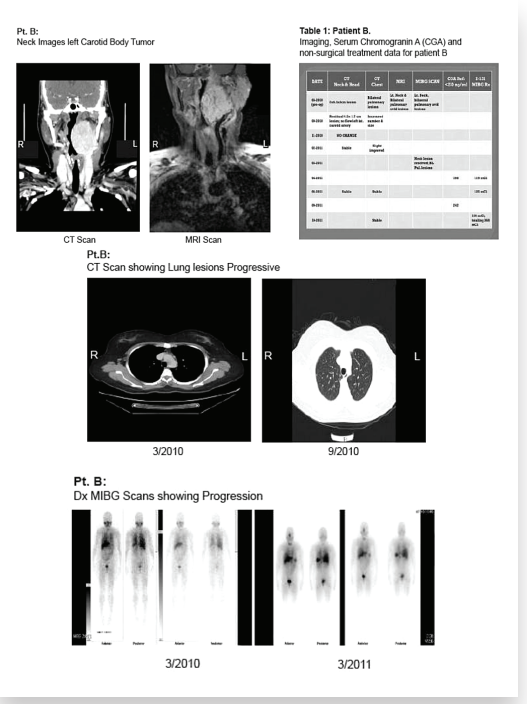
RESULTS

PATIENT A: A 48 year old man presented with an asymptomatic 6x4 cm right lateral neck mass that had been gradually increasing in size for the preceding 4 years. He was normotensive. The neck tumor was encasing the right common carotid artery and its branches, causing marked splaying of the internal & external carotid arteries. There were multiple bilateral pulmonary nodules, multiple hypervascular liver lesions, with intense enhancement after gadolinium administration, multiple abnormal foci throughout the thoracic spine with particularly hot uptake in L1, L3 & L4 , left glenoid fossa, right 12 th rib. The MIBG scan was negative. Urine metaneprine 0.4 umol/day (Ref. Range:0-1.49) normetanephrine 0.92 umol/d (0- 3.43). Two sessions of tumor embolization for 2 consecutive days followed by the resection of a highly vascular carotid body tumor was done that required 5 hours and 4 units of blood transfusion.

Postoperatively, hypoglossal nerve palsy and mild hoarseness of voice were noted with eventual complete resolution. Postoperatively patient received external beam radiation therapy (EBRT) for the vertebral lesions. US guided FNA of the liver lesion showed metastatic neoplasm consistent with neuroendocrine tumor. The hepatic lesions were radiofre-quency-ablated. For octreotide avid lesions

PRRT approval by Ethics committee is awaited. At 72 months he has remained in remission of neck lesion, stability of liver & bone lesions with stable serum CGA.





PATIENT B: A 39 years old lady had resection of a highly vascular left cervical CBT. Intraoperatively, she had to receive 4 units of blood along with the repair of the surgical tear in the internal carotid artery without sequlae. Her clinical, imaging, serum CGA data along with the non-surgical treatment rendered to her are depicted in table1.

Her tumoral Ki-67 index was 3% . She had diffuse MIBG avid lung lesions and received 368 mCi 1-131 MIBG in 3 sessions. At 6 months follow up the lung lesions are stable with stable serum CGA.

CONCLUSIONS: Carotid body tumors (chemodectomas) should be considered in evaluation of a lateral neck mass. A complete surgical resection with reversible neurovascular complications of large and neglected cervical malignant paraganglioma is possible in experienced hands.

Distant metastases can be managed using EBRT to skeletal lesions, radiofrequency ablation for liver metastases and 1-131 MIBG when scan shows tracer avid lesions, resulting in short/long term stability. A longer follow up course and a wider experience is needed to define the natural history and most effective management for CBTs. Approval of PRRT & refinement in therapy are urgently needed.

PROJECT TITLE: **Management Of An Advanced Pancreatic Tumor**

RAC # 2110 192

INVESTIGATORS: *Mohammed Ahmed, MD, Hindi Al-Hindi, MD*

PROJECT DESCRIPTION

INTRODUCTION: Pancreatic neuroendocrine tumors (NET) are rare encounters, representing about 1.3%of all pancreatic cancers in incidence and 10% in prevalence (1). However, increased awareness has resulted in an increased incidence and prevalence.

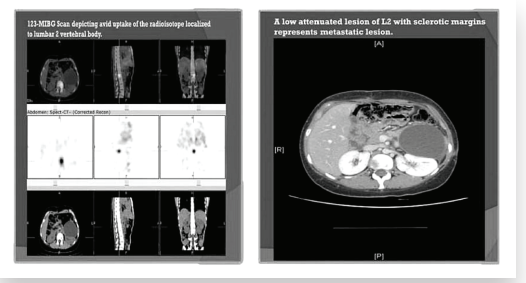
They are classified as either functional (10–30%) or non-functional (50–80%) (2). Majority of patients present at an advanced stage and the overall prognosis and survival remains pessimistic. However, advances in the treatment of malignant pancreatic NETs have provided optimism. Recent reports of the results use of tyrosine kinase inhibitor, sunit-inib and mTOR inhibitor, everolimus hold promise for patients with malignant pancreatic NETs.

Notwithstanding these developments, and the availability of an array of treatment modalities, there has been alack of information regarding a clear algorithm of optimal treatment or the sequence in which various treatment modalities can be applied for a given patient.

AIMS: We report a young lady with asporadic large nonfunctioning invasive pancreatic NET that disseminated to regional lymph node and vertebra. We suggest an algorithm consisting of Whipple's procedure followed by concurrent use of radionucleide (when applicable), cyberknife stereotactic radiosurgery and suggest the addition of everolimus for similar cases.

MATERIALS AND METHODS: A 20 year old female was referred to us post-Whipple procedure for a pancreatic NET. We undertook histological examination of the tumor tissue, whole body 123- MIBG scan, whole body PET-CT, CT abdomen, Octreoscan, serum chromogranin (CGA) and genetic analysis study.

RESULTS: The tumor was 8 cm, with lymphovascular, duodenal wall, adjacent liver tissue, and metastatic celiac lymph node inva-sion. Imaging results showed destructive lesion of L2 vertebral body with avid uptake of MIBG, but not the FOG iso-tope. Serum CGA was 114 ng/ml (normal <225). Full length gene



sequencing was done for detection of mutation or deletion for succinic dehdrogenase B, C, D and for VHL; these studies turned out to be negative. She has received 157 mCi 1-131 MIBG followed by cyberknife stereotactic radiosurgery consisting of 30 Gys in 5 fractions directed to the vertebral lesion. The use of everolimus is under consideration.

CONCLUSIONS: The case is illustrative of Pancreatic NETs being diagnosed at an advanced stage presenting with metastases. Treatment options are limited for these patients. Recently evidence has emerged with favorable outcome using everolimus. We suggest a multimodal approach as outlined above with consideration for the use of everolimus in similar cases.

References:

1. Yao, JC, Shah MH, Tetsuhlde I, et al: Everollmus for Advanced Pancreatic Neuroendocrine Tumors. N Engl J Med 2011:364;514- 523.
2. Jensen RT, and Delle Fave, G: Promising Advances In the Treatment of Malignant Pancreatic Endocrine Tumors. N Engl J Med 2011:364;564-565

NURSING AFFAIRS

NURSING AFFAIRS

ASSISTANT CHIEF
Helen Redekopp

NURSING RESEARCH DIVISION
Muna Anani, RN, CDE, PhD
Sofia Macedo, RN, BSN

NURSING AFFAIRS IS COMMITTED TO CONDUCTING HIGH-QUALITY research that transforms nursing practice at KFSH&RC. Nurses are encouraged to develop research proposals, conduct research in teams and to disseminate research findings. Nursing Affairs provides continuous support for nurses in order to facilitate involvement in research, including the Nursing Research Council and a Nursing Research Mentorship Program. Supporting nurses in their quest for new knowledge plays an important role in the professional development of individual nurses and the nursing profession.

As part of the Nursing Affairs commitment to expand the Research Program, the Nursing Research Division was created in October 2011 and is composed of an Education Coordinator and 3 Clinical Instructors. These individuals play an integral role in expanding the nursing research profile internally and externally of the King Faisal Specialist Hospital and Research Centre. By the end of 2011, the team started to plan the First Annual Nursing Research Awareness Day for 2012. Nursing Affairs continually pursues the translation of high quality research into nursing practice, which is paramount to improving patient care delivery.

RAC APPROVED RESEARCH ACTIVITY

PROJECT TITLE: **Use of Double Lumen Central Venous Catheters (DLCVC) for the Drainage of Pleural Effusion in Pediatrics: A Prospective Observational Pilot Study**

RAC # 2101 072

INVESTIGATOR: *N. Shwaihet*

PROJECT DESCRIPTION: This prospective observational study came about due to the placement of double lumen central venous catheters for pleural drainage in pediatrics post cardiac surgery. The literature was not available to draw any conclusions regarding the safety or efficiencies of such devices. The investigators designed this study to measure the safety and efficiency of central venous catheters for pleural drainage in pediatric patients (aged newborn to 5 years) with the purpose of informing patient care decision making at the bedside.

PROGRESS AND MAJOR FINDINGS: This study is currently in the data analysis phase. At this stage 49 patients were enrolled and that 2 patients were excluded. The patients range is from 7 days to 4 years of age. 28 patients had the CVC line inserted on the right side and 10 on the left side and 9 were not recorded. The preliminary results allow us to say that the incidence of pleural effusion within 24h post line removal was 0% and the incidence of pleural effusion after 24h post line removal was 8.51%. The use of DLCVC was safe and effective in draining pleural fluids and it may be used to treat pneumothorax.

PROJECT TITLE: **Humidified oxygen versus air for the treatment of Chemotherapy/Radiation therapy induced mucositis**

RAC # 2101 084

INVESTIGATORS: *G. Ingram, A. Amro, J. Ordonio, W. Peterson, C. Rodriguez*

PROJECT DESCRIPTION: Oncology induced mucositis is a painful, 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: The project is in data collection phase and has included 16 patients in the study. Progress Report is to be submitted April 2012.

PROJECT TITLE: **Nursing education and the impact on patient outcomes: A Randomized Control Trial**

RAC # 2101 063

INVESTIGATORS: *V. Farquhar, G. Ingram, B. Foreman*

PROJECT DESCRIPTION: Nursing education departments are constantly under scrutiny when resources in patient care organizations are tight. This randomized control trial was designed by the researchers to expand the evaluation of nursing education in an acute care hospital setting. In this study nursing education is being evaluated on four levels, incorporating basic evaluation of the education program right through to the impact on patient outcomes.

PROGRESS: This study is under data analysis phase.

PROJECT TITLE: **Risk Factors for Surgical Site Infection in Colorectal Surgery in Saudi Arabia**

RAC # 204 071

INVESTIGATORS: *D. Hibbert, N. Al-Sanea, A. Abdul Jabbar, N. Elkum*

PROJECT DESCRIPTION: This prospective observational trial was designed to evaluate risk factors for surgical site infection in colorectal surgery in Saudi Arabia.

PROGRESS AND MAJOR FINDINGS: Data analysis is completed and this study highlighted the impact of preoperative nutrition and obesity, specifically abdominal obesity in the development of surgical

site infection. The study is now being written up for publication.

PROJECT TITLE: **Working with Sick Children and families in hospital: the experience of expatriate nurses working in Saudi Arabia**

RAC # 2111 066

INVESTIGATOR: *T. Rowsell*

PROJECT DESCRIPTION: An emerging global reality is the presence of a culturally diverse workforce in healthcare environments. Saudi Arabia is one of the countries that attract nurses from all over the world and from different cultural, ethnic and educational backgrounds. The proposed study will use hermeneutic phenomenology informed by van Manen, to explore and gain deeper understanding in the meaning of working with hospitalized children and their families through interpreting the everyday lived experiences of expatriate nurses in Saudi Arabia. Data will be collected by semi or unstructured interviews with eight-to-ten nurses who are non-Saudi citizens. Data analysis will occur using van Manen's identified six hermeneutic phenomenological research activities (entwining research processes of reflecting, reading and writing) to identify themes that describe the phenomenon.

PROGRESS: Data collection to be initiated.

PROJECT TITLE: **Survey of KFSH&RC&RC: Perceived effect of Working Overtime**

RAC # 2101 073

INVESTIGATOR: *D. Espada*

PROJECT DESCRIPTION: This study aims to determine the effects of overtime on the quality of nursing care, assess the effects of working overtime on the well-being of the person, and determine if working overtime increases the risk of committing errors.

PROGRESS AND MAJOR FINDINGS: Data collected in 397 participants revealed that the problems identified by the nurses themselves as effect of doing frequent voluntary and/or mandatory overtime are less time with family, sleep disturbance and having inadequate sleep. One third of the population also identified that they have seen colleagues experiencing errors in medication administration, frequently being absent from work, reporting late for work and inability to cope with stress. Policy makers should then consider condition variables to see the effects of working overtime closely and make a change in nursing practice. The study supports the need to minimize staff shortage by staff augmentation thus affecting amount of overtime in a unit.

PROJECT TITLE: **Experiences of patients who have children with cleft lip and/or palate seeking treatment at the KFSH&RC**

RAC # 2081 028

INVESTIGATOR: *D. A. Al Rub*

PROJECT DESCRIPTION: To describe the experiences of parents who have children with cleft lip or palate seeking treatment in our institution.

PROJECT PROGRESS AND MAJOR FINDINGS: This study provides important insights into parent's needs. Parents presented with a great variety of needs. These needs started from delivery and maternity ward, the parents interviewed indicated that there were a lack of emotional support, reassurance and communication with health care professionals. Their major issue was feeding. We believe that feeding counseling should begin at that time. On the other hand it would be good if feeding services were available on the maternity ward. The primary care management begins at the time of diagnosis that usually occurs at birth. Gaining insight into what this transition means to these parents can give health care professionals a better understanding of the parent's experience and help them to develop a plan of care that is supportive and to meet their expectations. Furthermore, more education for health care professionals is needed to enable them to give appropriate guidance and support to the parents.

PROJECT TITLE: **To investigate factors affecting critical care nurses compliance with hospital policy regarding double checking of high alert medications (Narcotics)**

RAC # 2081 051

INVESTIGATORS: *Z. Jaffer; K. Kardesh*

PROJECT DESCRIPTION: This study meant to investigate factors affecting the decision to make nurses comply with hospital policy regarding double checking of high alert medication (Narcotic) in KFSH&RC

PROGRESS AND MAJOR FINDINGS: The study involved 20 nurses (11 female and 9 male) working in the five critical care units of the KFSH&RC. The nurses ranged from 32 to 52 years of age. The reasons for medication error were divide into work environment, human error and lack of efficiency. 75% of all medication errors in the study were related to wrong timing or missed medication. It is observed that the scope for error increase as the complexity of the medication to be administered increases. Errors with regards to temporality and routes of administration were potentially dangerous but more so were the errors of omission and delayed administration.

ONCOLOGY CENTRE

ONCOLOGY CENTRE

DIRECTOR
Mohammed Mohiuddin, MD

DEPUTY DIRECTOR
Mahmoud Aljurf, MD

KFSH&RC ENJOYS THE RECOGNITION OF HAVING THE LARGEST cancer facility in the Gulf region where more than 3,500 new patients are treated annually. 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 centres 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 Centre's Research Unit which also serves as a hospital base for cancer and bone marrow transplantation registries. Major achievements for the year include:

- Continued membership of the CBMTG (Canadian Bone Marrow Transplantation Group) and the EBMT Clinical Trials Group (EBMTG); Highest accruing institution on CBMTG protocol 0601.
- Continued institutional membership and collaborative studies with Southwest Oncology Group (SWOG), American College of Radiology Imaging Network (ACRIN), and Radiation Therapy Oncology Group (RTOG).
- Several collaborative studies started with RTOG. Highest accruing institution on RTOG protocol 0417.
- Eastern Mediterranean Blood & Marrow Transplantation Group (EMBMT) expanded. Thirteen Disease site working Committees formed. Several research protocols in progress. Fifth article published in Bone Marrow Transplantation Journal.
- Several new research studies started and significant numbers of papers were published.
- Gulf Oncology Regional Group (GORG) expanded in KFSH&RC. The first successful study, GORG-001, completed. Second multicenter breast study, GORG-002, is in progress.

- Continue to receive investigational drugs from National Cancer Institute (NCI) for patients on clinical trials.
- Intensity Modulated Radiation Therapy (IMRT) credentialing by Radiological Physics Center (RPC) at MD Anderson Cancer Center, USA. IGRT credentialing is in progress.

FUTURE RESEARCH DIRECTION

- Promote well designed clinical/translational research activities.
- Establish firm collaboration and team work with Research Centre and other local, regional and international groups to promote translational research.
- Continue membership and collaboration with national, regional and international clinical research cooperative groups.
- Expand and maximize utilization of available databases for certain tumor sites in research direction and benchmarking.
- Establish refresher courses for Clinical Research Coordinators to achieve CCRP certification.
- Spearhead more international multi-centre clinical research trials in collaboration with international cooperative groups like RTOG, SWOG, ECOG, CBMTG, EBMT and ACRIN 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 Culturally Sensitive Quality of life (QOL) trials.
- Serve as a University Hospital Clinical research platform for the affiliated "Alfaisal" University College of Medicine.

PROJECT TITLE: **A Randomized Phase III Trial of CC-5013 (Lenalidomide, NSC-703813) and Low Dose Dexamethasone (LLD) Versus Bortezomib (PS-341, NSC-681239), Lenalidomide and Low Dose Dexamethasone (BLLD) for Induction, in Patients with Previously Untreated Multiple Myeloma Without an Intent for Immediate Autologous Stem Cell Transplant**

RAC # 2081 113

INVESTIGATOR: *F. Alsharif, N. Chaudhri*

PROJECT TITLE: **Phase III Trial of LHRH Analog Administration During Chemotherapy to Reduce Ovarian Failure Following Chemotherapy in Early Stage, Hormone-Receptor Negative Breast Cancer**

RAC # 2091 013.

INVESTIGATOR: *A. Al Sayed*

PROJECT TITLE: **A Multicenter Prospective Phase II Trail of Neo-Adjuvant(FEC 100)/Cisplatin-Docetaxel ±Trastuzumab in women who over expressed or amplified Her2/neu with Locally Advanced Breast Cancer**

RAC # 2061 048

INVESTIGATOR: *T. Twegieri*

PROJECT TITLE: **Randomized phase III trial to determine the effectiveness of Vitamin D3 (Cholecalciferol) given with Docetaxel versus Docetaxel in patients with metastatic breast cancer**

RAC # 2091 009

INVESTIGATOR: *T. Twegieri*

PROJECT TITLE: **A Randomized Multicentre Study Comparing GCSF Mobilized Peripheral Blood and GCSF stimulated Bone Marrow in patients Undergoing Matched Sibling Transplantation for Hematologic Malignancies**

RAC # 2081 076.

INVESTIGATOR: *M. Aljurf*

PROJECT TITLE: **A phase II study of Bevacizumab in combination with definitive radiotherapy and cisplatin chemotherapy in untreated patients with locally advanced cervical carcinoma**

RAC # 2081 012

INVESTIGATOR: *N. Al Rajhi*

PROJECT TITLE: **Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally Advanced Resected Head and Neck Cancer**

RAC # 2101 074.

INVESTIGATOR: *N. Al Rajhi*

PROJECT TITLE: **Phase II trial of dasatinib in patients with recurrent glioblastoma multiforme**

RAC # 2081 013

INVESTIGATOR: *N. Al Rajhi*

PROJECT TITLE: **A Phase II Study of Postoperative Intensity Modulated Radiation Therapy (IMRT) with Concurrent Cisplatin and Bevacizumab Followed by Carboplatin and Paclitaxel for Patients with Endometrial Cancer**

RAC # 2101 016

INVESTIGATOR: *N. Al Rajhi*

PROJECT TITLE: **Phase II/ III Study of Image–Guided Radiosurgery/SBRT for Localized Spine Metastasis**

RAC # 2091 073

INVESTIGATOR: *N. Al Rajhi*

PROJECT TITLE: **Prospective Data Collection of Newly Diagnosed Hodgkin's Disease and Non-Hodgkin's Lymphoma Cases**

RAC # 2021 048

INVESTIGATOR: *S. Akhtar, Ewings*

RAC # 931 035

INVESTIGATOR: *M. Memon*

PROJECT TITLE: **Positron Emission Tomography/Computerized Tomography in the Initial Staging of Locally Advanced Breast Carcinoma**

INVESTIGATOR: *T. Twegieri.*

PROJECT TITLE: **A Randomized Phase II Study Comparing Pemetrexed Plus Best Supportive Care witn Best Supportive Care as Maintenance, Following First Line Treatment with Pemetrexed-Cisplatin in Patients with Advanced Non-Small Cell Lung Cancer (ALIMTA Study)**

RAC # 2071 073

INVESTIGATOR: *H. Husseini*

PROJECT TITLE: **A Worldwide Observational Registry collecting Longitudinal data on the management of CML patients in routine practice**

RAC # 2081 025

INVESTIGATOR: *N. Chaudhri*

PROJECT TITLE: **Retrospective Database for Lymphoma patients infected with Hepatitis B Virus/Hepatitis C Virus who received Cytotoxic Chemotherapy: Outcome, Incidence of Hepatitis Reactivation, Identification of Risk Factor and Duration of Lamivudine Prophylaxis for Prevention of HBV Reactivation**

RAC # 2071 072

INVESTIGATOR: *A. Al Zahrani*

PROJECT TITLE: **The Combination of GnRh Analogue and Aromatase Inhibitor in Receptor Positive Premenopausal Women with Advanced Breast Cancer A Prospective Trial**

RAC # 2081 064

INVESTIGATOR: *A. Al Sayed*

PROJECT TITLE: **An Open-Label, Multicenter, Expanded Access Study of RAD 001 in Patients with Metastatic Carcinoma of the Kidney who are Intolerant or have Progressed Despite Any Available Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy (REACT)**

RAC # 2081 094

INVESTIGATOR: *S. Bazarbashi*

PROJECT TITLE: **Phase II Prospective Study of the Clinical Efficacy of Autologous SCT in patients with Critical Limb Ischemia**

RAC # 2081 026

INVESTIGATOR: *H. Al-Zahrani*

PROJECT TITLE: **A Phase I-II Trial of Capecitabine (Xeloda), Oxaliplatin and Irinotecan in Combination with Bevacizumab in 1st Line Treatment of Metastatic Colorectal Cancer**

RAC # 2081 068

INVESTIGATOR: *S. Bazarbashi*

PROJECT TITLE: **Phase II Study of Vincristine, Adriamycin, Actinomycin, Ifosfamide Combination Chemotherapy in Ewing's Sarcoma**

RAC # 2031 065

INVESTIGATOR: *M. Memon*

PROJECT TITLE: **Establishment of Acute Lymphocytic Leukemia Data Base in the Department of Oncology**

RAC # 2021 051

INVESTIGATOR: *N. Chaudhri*

PROJECT TITLE: **Data Collection of Newly Diagnosed Breast Cancer Cases (2007)**

RAC # 2051 029

INVESTIGATOR: *D. Ajarim*

PROJECT TITLE: **Establishing a Database for Aplastic Anaemia and Other Marrow Failure Syndrome**

RAC # 2021 084

INVESTIGATOR: *H. Al Zahrani*

PROJECT TITLE: **Functional Assessment of Cancer Therapy–Bone Marrow Transplant**

RAC # 2071 079.

INVESTIGATOR: *A. Al-Zahrani*

PROJECT TITLE: **Sarcoma Database**

RAC # 2081 015

INVESTIGATOR: *M. Memon*

PROJECT TITLE: **A pilot trial of pre-operative chemotherapy using capecitabine (Xeloda), external beam radiation and cetuximab (Erbitux) followed by definitive surgery in patients with localized (non-metastatic) rectal cancer**

RAC # 2071 051

INVESTIGATOR: *S. Bazarbashi*

PROJECT TITLE: **The prognostic significance of BCL2 & BCL6 expression in DLBLC treated by CHOP or R_CHOP. Retrospective study, single institute experience**

RAC # 2071 061

INVESTIGATOR: *H. Soudy*

PROJECT TITLE: **Prospective phase II study of rabbit anti-thymocyte globulin (ATG, Thymoglobuline®, Genzyme) with Cyclosporin for patients with acquired aplastic anaemia and comparison with matched historical patients treated with horse ATG and cyclosporin: A study from the European Blood and Marrow Transplant (EBMT) severe aplastic anaemia working party (RATGAA07)**

RAC # 2081 005

INVESTIGATOR: *H. Al-Zahrani*

PROJECT TITLE: **A Multi-national, Randomized, Phase III, GCIG Intergroup Study Comparing Pegylated Liposomal Doxorubicin (CAELYX®) and Carboplatin in Patients with Epithelial Ovarian cancer in late Relapse (>6 months)**

RAC # 2051 062

INVESTIGATOR: *A Al Jubran*

PROJECT TITLE: **Nasopharyngeal Carcinoma Database**

RAC # 2051 017

INVESTIGATOR: *N. Al Rajhi*

PROJECT TITLE: **Autologous Peripheral Blood Stem Cell Transplantation within Vivo Purging as an Alternate Stem Cell Transplantation Program for Patients with Acute Myelogenous Leukemia (AML) in First (CR1) and Second (CR2) Complete Remission with no HLA Matched Related Donor**

RAC # 2001 044

INVESTIGATOR: *F. Al Mohareb*

PROJECT TITLE: **Induction of Mixed Hematopoietic Chimerism in Patients Using Fludarabine, Low Dose TBI, PBSC Infusion and Post Transplant Immunosuppression with Cyclosporin and Mycophenolate**

RAC # 2001 051

INVESTIGATOR: *M. Aljurf*

PROJECT TITLE: **Prospective Database for Acute Myeloblastic Leukemia**

RAC # 2051 057

INVESTIGATOR: *N. Chaudhri*

PROJECT TITLE: **Prospective Database for Acute Chronic Myelogenous Leukemia**

RAC # 2051 056

INVESTIGATOR: *N. Chaudhri*

PROJECT TITLE: **Phase II Trial of Concurrent Administration of Intravesical BCG and Interferon 2-B in the Treatment and Prevention of Recurrence of Superficial Transitional Carcinoma of the Urinary Bladder**

RAC # 2011 073

INVESTIGATOR: *S. Bazarbashi*

PROJECT TITLE: **Outcome of Hemapoietic Cell transplantation (HSCT) for Severe Aplastic Anemia Using Fludarabine and Cytoxan**

RAC # 2091 014

INVESTIGATOR: *H. Al Zahrani*

PROJECT TITLE: **TP53 Mutations in locally advanced Breast Cancer in Saudi Arabia**

RAC # 2040 037

INVESTIGATOR: *T. Twegieri*

PROJECT TITLE: **Phase II study of Neo-adjuvant Chemotherapy with Doxorubicin Followed by Docetaxel-Cisplatin in Locally Advanced Breast Cancer**

RAC # 2011 022

INVESTIGATOR: *A. Ezzat*

PROJECT TITLE: **Phase II Study of Neo-adjuvant Intensive Sequential Chemotherapy with Adriamycin, Taxol, Cytoxan Followed by Mastectomy, Radiation, Tamoxifen in the Treatment of Locally Advanced Breast Cancer**

RAC # 981 020

INVESTIGATOR: *A. Ezzat*

PROJECT TITLE: **Cisplatin and RTX *vs* RTX- Ca of Cervix**

RAC # 951 024

INVESTIGATOR: *K. Balaraj*

PROJECT TITLE: **Post-operative adjuvant chemotherapy followed by adjuvant Tamoxifen vs nil for patients with operable breast cancer (EORTC)**

RAC # 931 005

INVESTIGATOR: *A. Ezzat*

PROJECT TITLE: **Pre-operative Chemotherapy in Operable Breast Cancer (93-108)**

RAC # 931 006

INVESTIGATOR: *A. Ezzat*

PROJECT TITLE: **ONE Registry: A prospective observational registry on the use of NovoSeven® (activated recombinant human factor Vlla) for on demand treatment of mild to moderate bleeds in haemophilia A and B patients with inhibitors**

RAC # 2091 019

INVESTIGATOR: *H. Al Zahrani*

PROJECT TITLE: **A multi-center, single arm, phase II study of adjuvant imatinib (Glivec™) in patients following the resection of primary gastrointestinal stromal tumor (GIST)**

RAC # 2091 053

INVESTIGATOR: *M. Memon*

PROJECT TITLE: **An Open-label, single arm, phase II trial of the combination of Trans-arterial chemoembolization (TACE) and Sorafenib in non Metastatic unresectable Hepatocellular carcinoma (HCC)**

RAC # 2091 040

INVESTIGATOR: *S. Bazarbashi*

PROJECT TITLE: **A randomized, open-label phase III Intergroup study: Effect of adding Bevacizumab to cross over flouropyrimidine based chemotherapy (CTx) in patients with metastatic colorectal cancer and disease progression under first line standard CTx / Bevacizumab com (ML 18147)**

INVESTIGATOR: *A. Al Jubran*

PROJECT TITLE: **Randomized Phase III trial of surgery alone or surgery plus preoperative Gemcitabine-Cisplatin in Clinical early stages (T2N0, T1-2N1, T3n) and (T3N1) Non-small cell lung cancer (NSCLC)**

RAC # 2031 059

INVESTIGATOR: *Kattan*

PROJECT TITLE: **EBMT/CLWP non-interventional prospective study on effects of 2nd generation TKI on outcome of allotx in CML**

RAC 2051 056

INVESTIGATOR: *M. Aljurf*

PROJECT TITLE: **Extending Molecular response with Nilotinib in newly diagnosed chronic myeloid leukemia (CML) patients in chronic phase (ENESTxtnd)**

RAC # 2101 102

INVESTIGATOR: *N. Chaudhri*

PROJECT TITLE: **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 (EVERMORE)**

RAC # 2101 002

INVESTIGATOR: *S. Bazarbashi*

PROJECT TITLE: **Multicenter, Phase III, randomized study to evaluate treatment customized according to RAP80 and BRCA 1 assessment in patients with advanced non-small-cell lung cancer (RAP 80)**

RAC # 2091 088

INVESTIGATOR: *H. Al Husseini*

PROJECT TITLE: **Combined Immunosupprresive Therapy for the Treatemnt of Aplastic Anemia: A Pilot Study**

RAC # 2041 008

INVESTIGATOR: *H. Al Zahrani*

PROJECT TITLE: **Use of 18F- Flourodeoxyglucose (FDG) Position Emission Tomography (PET) as a Predictor of Residual Disease and Subsequent Relapse in Patients with Non- Hodgkin's Lymphoma (NHL) and Hodgkin's Lymphoma (HL) undergoing High Dose Chemotherapy (HDC) and (ASCT)**

RAC # 2041 050

INVESTIGATOR: *S. Akthar*

PROJECT TITLE: **Biomarkers in Chronic Graft vs. Host Disease (CGVHD)**

RAC # 2101 101

INVESTIGATOR: *M. Aljurf*

ACADEMIC & RESEARCH DAY - 2011 ABSTRACTS

Medical Oncology

TITLE: Combination chemotherapy with capecitabine (C), irinotecan (I) oxaliplatin (O) and bevacizumab (B) (XELOXIRIA) as first line treatment of metastatic colorectal cancer (MCRC): Preliminary results of a phase I-II trial. King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

AUTHORS: *S. Bazarbashi, A. H. Aljubran, H. Soudy, A. Darwish, A. Eltigani, M. Nabil-Ahmed, W. Edesa, M. Almubarak, A. Abu sabaa, M. Shoukri*

FOLFOXIRI demonstrated tolerable toxicities and improved efficacy compared to FOLFIRI in MCRC in a phase III trial. Oral C has demonstrated similar efficacy to IV 5-FU and might substitute IV 5-FU in the FOLFOXIRI regimen.

METHODS: This is phase I-II prospective trial using fixed dosed of Capecitabine (C), Oxaliplatin (O) and Bevacizumab (B) in combination of escalating doses of Irinotecan (I) in metastatic and locally advanced unresectable CRC patients (pts). The objectives of the study were to define the recommended dose (RD) of I in combination with C, O and B, safety and efficacy of the combination. The planned treatment in the first 3 pts was: I 150 mg/sqm over 90 min on day 1, O 130 mg/sqm over 2-h on day 1, C 2,000 mg/sqm/day from day 1 to 14, and Bevacizumab 7.5 mg/kg over 30 min on day 1. Cycles repeated every 3 weeks. I dose was increased to 200 mg/sqm or C dose was decrease to 1300 mg/sqm/day in subsequent groups of 3 pts on the basis of the observed dose limiting toxicities (DLT).

RESULTS: Until today, 29 pts have been enrolled. We report here the results on the 1st 20 pts. Pts characteristic are: sex (M/F) = 12/8, PS (0/1/2) = 2/14/4, age (median/range) = 52/24-73 years, sites of disease (single/multiple) = 6/14. The DLT was G3-4 diarrhea that was observed in 2 out of 3 pts receiving I at 200 mg/sqm, The I recommended dose was 150 mg/sqm which continued as phase II trial. Grade 3-4 toxicities were: nausea and vomiting 26%, diarrhea 52%, neutropenia 16%, thrombocytopenia 5.3%, fatigue 21%. Response evaluation was done according to ITT analysis. 5 Pts were not assessable for response because of 2 or less cycles of chemotherapy (3 consent withdrawal, 2 grade 4 toxicity). One CR, and 8 PR were observed for an overall response rate of 45% (95%CI: 34-56%). Two had SD and 3 progressed. At a median follow-up of 10 months median PFS is 18.3 months and median OS was not reached.

CONCLUSIONS: XELOXIRIA is toxic with diarrhea being the DLT. The recommended dose of I is 150 mg/sqm. Recruitment will continue with reduction in the C dose to 1600 mg/sqm daily. Short follow up prohibits meaningful interpretation of efficacy.

TITLE: Molecular Classification of Breast carcinoma. Are we different?

AUTHORS: *Taher AL-Tweigeri, Asma Tulbah, Foud Al-Dayel, Adher Al Sayed, Dahish Ajarim*

Molecular classification of breast cancer has been proposed based on gene expression profiles of human tumors. Luminal, basal-like, normal-like, and erbB2+ subgroups were identified and were shown

to have different prognoses. Breast cancer comprises a remarkably diverse group of diseases in terms of presentation, morphology, biologic characteristics and clinical behavior. Currently, decisions about breast cancer treatment are based on certain clinicopathologic parameters that have been clinically validated and serve as a guide for the use of systemic therapy and prognostication. These include tumor size, lymph node stage and histologic grade, vascular invasion, histologic type, and the patients' age and menopausal status. In addition, a few molecular markers, namely, the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 gene (HER2), which have been proven to provide therapeutic predictive and prognostic value, are currently of central importance for the routine clinical management of breast cancer. These individual prognostic factors provide limited information on the biology of the disease because of the heterogeneity of breast cancers as well as the interrelationship among prognostic markers. Molecular classification of various cancers based on gene expression patterns from complementary DNA (cDNA) microarrays has recently been applied for the hierarchical clustering. Using cDNA microarray profiling studies, distinct tumor subtypes of invasive breast carcinomas have been identified, which are associated with different clinical outcomes, including luminal/estrogen receptor (ER)+, normal breast–like, Her2/neu+, and basal-like subtypes. Among these, the basal-like and Her2/neu+ subtypes are associated with poorer clinical outcomes than other types in Western countries. Molecular subtypes also proved to have significant predictive value for therapeutic response of breast cancer. Luminal cancers are generally hormone receptor-positive and appropriate for endocrine therapy. The HER2 subtype is suitable for targeted therapy such as trastuzumab. Basal subtypes are resistant to current targeted therapies for breast cancer, but may be responsive to therapies targeted against EGFR. Studies showed that ER-negative tumors benefit from chemotherapy at twice the rate of ER-positive tumors and that ER-positive tumors are less responsive to neoadjuvant chemotherapy. The prevalence, clinicopathologic features of each breast cancer subtype in 374 patients with invasive breast carcinoma stage I-III, non metastatic, diagnosed between 2001 to 2006 will be presented. The subtyping is based on immunohistochemical staining performed on constructed tissue microarrays using known antibodies for basal and luminal-type epithelia.

TITLE: The use of Cone Beam CT for Evaluation of RT Target (PTV) and OAR volumes in Pediatric Abdominal Neuroblastoma

AUTHORS: *Mohamed SN El Beltagi, MD & Yasser Khafaga, MD*

ABSTRACT

PURPOSE: To quantify the interfraction organ motion relative to bone in different breathing states during abdominal IMRT in pediatrics through the use of CBCT for better PTV and PRV margins definition.

METHODS AND MATERIALS: This is a retrospective study in which 32 images of KV CBCT for 6 pediatric patients with abdominal neuroblastoma treated with IMRT under general anesthesia (GA) has been revised. Planning CT scan was considered the basic position against which organs and target motions were evaluated. For each scan the position of both kidneys and the liver were assessed. The target movement has been evaluated in two patients who were treated for apparent gross residual disease.

RESULTS: The mean age of the patients was 3.9+/-1.7 years. The movement in the anteroposterior and mediolateral directions was limited to 2 mm. The range of target movement in the craniocaudal direction (CC) was 6 mm. The right kidney range of movement was 14mm while the left kidney movement range was 10 mm. It was clear that not all of these changes were related to the organ movement, as we noticed up to 6 mm change in the length of the kidneys between fractions. Similarly, the liver upper edge range of motion was around 14 mm while the lower edge range of motion was 18mm. changing PTV based on target movement data led to noticeable sparing of the critical structures.

CONCLUSIONS: With the use of daily CBCT we can limit the superior inferior margin to 5 mm and the other margins to 3 mm. If CBCT is not going to be used daily we should keep PTV margin 10 mm superior inferiorly and 3–5 mm in the other direction.

TITLE: Prevalence and genetypes' distribution of human papilloma virus in invasive cervical cancer in Saudi Arabia

AUTHORS: *Alsbeih G, Ahmed R, Al-Harbi N, Venturina LA, Tulbah A, Balaraj K.*

Biomedical Physics Department

ABSTRACT

OBJECTIVE: Data concerning HPV infection in cervical cancer are globally lacking in Saudi Arabia. Therefore, the aim of this study was to assess HPV prevalence and genotypes' distribution in invasive cervical cancer in our patients to provide baseline information for screening and prevention.

METHODS: The study included 100 paraffin-embedded cervical tumors. HPV genotyping was performed using the Linear Array kit (Roche Diagnostic) that enables the concomitant detection of 37 mucosal HPVs including 13 most common high-risk viruses.

RESULTS: Eighty-nine specimens were HPV-positive. Eleven different HPV genotypes were detected, 8 high risk (16, 18, 31, 39, 45, 51, 59, 73) and 3 low risk (6, 64, 70). Ten patients had double infections involving mainly HPV-16 and 18. The most common genotypes were 16 (65.2%), 31 (7.9%), 45 (6.7%), 18 (3.4%), and 73 (2.3%). However, by considering double infections, HPV-18 became the second most common genotype (10.1%). The patients' median age was significantly lower (P=0.028) in HPV-16/18 infected group compared to other genotypes (44, range 32–76 vs. 49, range 38–67).

CONCLUSIONS: Eighty-nine percent of cervical cancers in Saudi Arabia were associated with HPV infection, and 78.7% (70/89) of HPV-positive tumors were infected with HPV-16/18, which caused the cancer to appear 5years earlier than the combined HPV-negative and other HPV genotypes (P=0.013).

TITLE: Central Nervous System Metastases of Primary Breast Cancer Origin: Retrospective Analysis of 200 Cases

AUTHORS: *Medhat El-Sebaie, Dahish Ajarim, Taher AlTwegeri, Adher AlSayed, Mohammah AlShabanah, Ehab Mohd Khalil –Abdelrahman, Mahmoud AbdAlsalam, Mohamed Nabiel, Alaa Darwirsh and Ameen AlTegani*

ABSTRACT

Breast cancer is the second most common cause of CNS metastases, and is the solid tumor most commonly associated with leptomeningeal metastases. The incidence of clinically evident brain metastases among women with stage IV breast cancer is estimated to be 10% to 16%. These figures underestimate the true incidence, given that brain metastases are found in 30% of patients at autopsy. The prognosis of patients with brain metastasis remains poor. Several factors are reported to increase the risk of brain metastasis, including young age, poor performance status, lung metastases, estrogen receptor (ER) negative tumors, and high burden of metastatic disease. Several studies suggest an increased risk of brain metastasis in HER-2overexpressing tumors. Between March 2001 and March 2011, more than 200 cases with primary breast cancer diagnosed with brain metastases were involved in this study. All cases were reviewed to address the risk factor(s) that could be associated with the development of brain metastases. This review will provide unyielding information about the most important risk factors/predictor factors to develop brain metastases in breast cancer patients.

TITLE: The Pattern of Antimicrobial Use for Palliative Care In-Patients during the Last Week of Life

AUTHORS: *Mohammed Abduh Al-Shaqi, MBBS, DCH, ABFM, PallCM, Ahmad Hasan Alami, Rph, Ali Saeed Al-Zahrani, MD, PhD, Batlah Al-Murshed, Abdulrahman Bin-Muammar, Mohammad Zafir Al-Shahri, MBChB, ABFM, FFCM, ABHPM*

ABSTRACT

BACKGROUND: In terminally-ill cancer patients approaching the dying phase, liberal use of antimicrobials is often viewed by palliative care experts as irrational. No previous reports have reviewed current antimicrobial use in palliative care settings in Saudi Arabia.

OBJECTIVE: The objective of this study was to explore the pattern of antimicrobial use in a tertiary palliative care unit (TPCU) during the last week of patients' life.

METHODS: Medical records of all patients who died in the TPCU over a 14 month period were reviewed for demographics as well as the frequency and rationale of antimicrobial use during the patients' last week of life. Information on antimicrobial use was obtained from a computerized pharmacy database.

RESULTS: Of 138 patients who died with advanced cancer in the TPCU, 87 (63%) were on one or more antimicrobials during their last week of life. Antibiotics were more frequently used as compared to antifungal and antiviral agents, 64 (46.4%); 45 (32.6%); and 2 (1.5%), respectively. About one third (31.3%) of patients who received antibiotics during their last week of life were prescribed more than one antibiotic. Antimicrobials were mostly given systemically (79%) rather than topically (21%). The most common rationales for antimicrobial prescribing were oral thrush in 36 patients (25.4%), wound care in 29 patients (20.4%), and on empirical basis in 29 patients (20.4%).

CONCLUSIONS: The current practice of antimicrobial prescribing, especially for patients who are eminently dying may need to be reviewed. Initiation of antimicrobial treatment in this group of patients should be based on clear treatment goals and desired outcomes, considering views of patients and families.

ORGAN TRANSPLANT CENTER

ORGAN TRANSPLANT CENTER

DIRECTOR
Dieter Broering, MD

THE ORGAN TRANSPLANT CENTER (OTC) IS A NEWLY ESTABLISHED division of the KFSH&RC to provide world leading transplantation healthcare. We are in the phase of establishing to conduct top notch interdisciplinary Research Centre of excellence to enable the translation of our findings to clinical settings which will have a significant potential clinical impact from improving the health, quality of life and life expectancy of transplant recipients to reducing cost of lifelong therapy.

Research at the OTC is a collaborative effort with the Research Centre of KFSH&RC and will be focusing on translational, epidemiological and clinical research in organ conditioning, tissue engineering, tolerance induction, medical and surgical innovations and stem cell research.

The year 2011 is only the beginning of our research endeavor as it is also the first year of being a division providing healthcare for kidney, liver, lung, pancreas and small bowel transplant patients and donors.

RESEARCH PROJECTS

PROJECT TITLE: **Organ Transplant Registry**

RAC No. 2121012

INVESTIGATORS: *Prof. Dieter Broering, MD, PhD, FEBS, (PI), Dr. Khaiid Al Meshari, MD, Mohammed Al Sebayel, MD, Shazia Subhani*

PROJECT DESCRIPTION: The Organ Transplant registry is a web-based registry designed in collaboration with Registries Core Facility, BESC department. This registry comprise of kidney, liver, lung, pancreas and small bowel recipients and donors related information. The registry also allows collaboration from regional hospitals and hospitals in neighboring countries as the need arises.

RATIONALE: To monitor the activities of the Organ Transplant Center (liver, kidney, pancreas, small bowel and lung transplantations) in KFSH&RC and to compare the outcomes of innovative surgical and therapeutic approaches with standard ones.

STATUS: Ongoing: development phase for liver and kidney transplants (testing phase for lung transplant Registry)

OTC - DEPARTMENT OF KIDNEY AND PANCREAS TRANSPLANTATION PUBLICATIONS

- Almeshari K, Pall A, Chaballout A, Elgamal H, Almana H, Alzayer F, Abaalkhail N, Altalhi M. Targeted Monitoring of Humoral Alloimmunity (Donor-Specific HLA Antibodies) Following Renal Transplantation. *Clinical Transplant* 2011.
- Safety and Efficacy of Peginterferon Alfa-2a Plus Ribavirin Combination Treatment in Chronic Hepatitis C Post –Renal Transplant patients. Sanai F, Bzeizi K, Almeshari K, Mousa D, Alashgar H, AlShoail G, AlMadani A, Aleid H. Oral presentation in American Transplant Congress April 30-May 4, 2011.

POSTER PRESENTATION

- Almeshari K, Pall A, Elgamal H, Alzayer F, Alawwami M. Preformed and De Novo HLA DQα Antibodies Cause AMR in Renal Allografts. 37th Annual Meeting, ASHI, 17-21 October 2011, Louisiana, USA.

ORAL PRESENTATIONS/INVITED SPEAKER

- Antibody Mediated Rejection. 2nd Gulf Cooperation Council (GCC) Organ Transplantation Congress for Organ Transplantation. 03-06 OCT 2011, Riyadh. K. Al Meshari.
- HLA and Immunogenetics Pre-congress Workshop. 2nd Gulf Cooperation Council (GCC) Organ Transplantation Congress for Organ Transplantation. 03-06 OCT 2011, Riyadh. K. Al Meshari.
- Impact of Sensitization on Transplant Programs. Recent Advances in Kidney Transplantation. Kuwait, 25–28 JAN 2011. K. Al Meshari.
- ABO Incompatible Kidney Transplantation. Recent Advances in Kidney Transplantation. Kuwait, 25–28 JAN 2011. K. Al Meshari.
- Post-Transplant Malignancies. 5th ISN Update Course in Nephrology. Dubai, UAE, 09-12 DEC 2011. K. Al Meshari.
- HLA DQ Antibodies are the Most Frequent Antibodies Encountered in Antibody-Mediated Rejection (AMR) of Renal Allografts. 37th Annual Meeting, ASHI, 17-21 October 2011, Louisiana, USA. AlMeshari K, Pall A, Elgamal H, Alzayer F, Alawwami M.
- Safety and Efficacy of Peginterferon Alfa-2a Plus Ribavirin Combination Treatment in Chronic Hepatitis C Post-Renal Transplant patients. Sanai F, Bzeizi K, Almeshari K, Mousa D, Alashgar H, AlShoail G, AlMadani A, Aleid H. American Transplant Congress April 30–May 4, 2011.

RESEARCH PROJECTS

PROJECT TITLE: **Determination of the effect(s) of polymorphism(s) in specific genes controlling the immune responses in Saudi renal transplant patients. 2006-2011**

RAC # 2041 081 / KACST AT-25-41

INVESTIGATORS: *Dr. Khalid AlMeshari (PI), Dr. Abdelghani Tbakhi, Dr. Khaled Al Hussein*

SPONSOR/COLLABORATOR: *KACST*

STATUS: Completed on DEC 2011

SUMMARY

Genotyping profiles of the natural killer cell immunoglobulin-like receptors (KIR) have been reported to vary among different ethnic groups. In this report for the first time, we commenced a longitudinal study to investigate the underlying immune system genes, which might contribute to the graft survival or rejection in Saudi population. We intended to identify new molecular markers in order to predict the presence or absence of detrimental factors underlying all immune responses in clinical transplantation. In addition, our main objective is to compare KIR distribution between kidney transplant donors and recipients. 30-kidney transplant donor and 30 recipients were genotyped and compared so far. All had the different KIR loci. As for the time being, we analyzed limited number of donors and recipients, samples are examined. Similar to most published data, we observed the dominance of the two framework genes 3DL2 and 3DL3 which are present in all (100%) recipients and donors investigated so far. While the other KIR genes vary in their frequencies. We also observed the predominance of AA1 genotype as observed previously in Lebanese and Palestinians. Moreover, the allelic distribution of all polymorphisms in the Saudi population was very close to that in the geographically and historically closest population in the Middle East the Lebanese and the Palestinians populations. In addition, a polymerase chain reaction with sequence-specific primers was used to genotype polymorphisms within genes encoding IFN-γ, TGF-β, TNF-α, IL-6, and IL-10 in a sample of 27 donors / recipients' pairs. While we are compiling data of cytokines gene polymorphisms, KIR genotyping and HLA matching with clinical follow up of recipients' post-transplant period, an appropriate statistical analysis will be performed after the entire samples are examined.

PROJECT TITLE: **Tuberculosis post solid organ transplantation, single center retrospective study**

RAC # 2121 074

INVESTIGATORS: *Dr. Hasan Al Eid (PI), Dr. Abdularhman Al Rajhi, Dr. Suad Mohammad, Dr. Abeed Pall and Dr. Faisal Abalkhail and Dr. Eid Al Mutairy*

STATUS: 2011–Ongoing.

ACADEMIC & TRAINING ACTIVITIES

Renal Transplant Fellowship Program accredited by the American Society of Transplantation (AST)

OTC–DEPARTMENT OF LIVER AND SMALL BOWEL TRANSPLANTATION & HEPATOBILIARY PANCREATIC SURGERY

PUBLICATIONS

- Schulze M, Dresske B, Deinzer J, Braun F, Kohl M, Schulz-Jürgensen S, Borggrefe J, Burdelski M, Bröering DC. Implications for the usage of the left lateral liver graft for infants ≤10 kg, irrespective of a large-for-size situation--are monosegmental grafts redundant? *Transpl Int.* 2011 Aug;24(8):797-804. IF=3.211.
- Castro FA, Försti A, Buch S, Kalthoff H, Krauss C, Bauer M, Egberts J, Schniewind B, Broering DC, Schreiber S, Schmitt M, Hampe J, Hemminki K, Schafmayer C. TLR-3 polymorphism is an independent prognostic marker for stage II colorectal cancer. *Eur J Cancer.* 2011 May;47(8):1203-10. Epub 2011 Jan 14. IF= 4.944.
- Herrmann J, Junge CM, Burdelski M, Ganschow R, Scheibner S, Petersen KU, Fischer L, Broering DC, Adam G, Helmke K. Transcapsular Arterial

Neovascularization after Liver Transplantation in Pediatric Patients Indicates Transplant Failure. *Radiology*. 2011 Aug 24. IF=6.066.

- Settmacher U, Götz M, Rahmel A, Bärthel E, Schlitt H, Puhl G, Broering D, Lehner F, Fischer L, Paul A, Schmidt J, Nadalin S, Obed A, Heise M. Living donor liver transplantation in adults in the MELD era in Germany--a multicenter retrospective analysis. *Transpl Int*. 2011 Sep;24(9):904-11. doi: 10.1111/j.1432-2277.2011.01283.x. Epub 2011 Jun 11. IF=3.211.
- Walter J, Nier A, Rose T, Egberts JH, Schafmayer C, Kuechler T, Broering DC, Schniewind B. Palliative partial pancreaticoduodenectomy impairs quality of life compared to bypass surgery in patients with advanced adenocarcinoma of the pancreatic head. *Eur J Surg Oncol*. 2011 Sep;37(9):798-804. Epub 2011 Jul 20. IF=0.25.
- Minouchehr S, Radtke A, Sotiropoulos GC, Molmenti EP, Braun F, Hindennach M, Honarpisheh H, Cicinnati VR, Malagó M, Broering DC, Schroeder T. Drainage patterns of right and accessory hepatic veins: anatomical-functional classification derived from 3-dimensional CT reconstructions. *Hepatogastroenterology*. 2011 Sep–Oct;58(110-111):1664-9. doi: 10.5754/hge10348. IF=0.677.
- Radtke A., Sotiropoulos G. C., Molmenti E.P., Sgourakis G., Schroeder T, Beckebaum S., Peitgen H.-O, Cicinnati V.R., Broelsch C.E., Broering D.C. and Malago M. Transhilar Passage in Right Graft Live Donor Liver Transplantation: Intrahilar Anatomy and Its Impact on Operative Strategy. (in press) *American Journal of Transplantation*, 2011 Oct. IF=6.048.
- Herrmann J, Junge CM, Burdelski M, Ganschow R, Scheibner S, Petersen KU, Fischer L, Broering DC, Adam G, Helmke K. Transcapsular arterial neovascularization after liver transplantation in pediatric patients indicates transplant failure. Radiology. 2011 Nov;261(2):566-72. *Epub* 2011 Aug 24. IF=6.066.
- Harbeck B, Anlauf M, Klöppel G, Bröring D, Lehnert H, Mönig H. An unusual case of a retrorectal neuroendocrine tumor with high–and low-grade differentiation. *Int J Colorectal Dis*. 2011 Dec 17. IF=2.645.
- The Clinical Consequences of Utilizing DCD (Donation after Cardiac Death) Liver grafts into Hepatitis C Recipients. Mawardi M, Aba Alkhail F, Katada K, Levstik M, Quan D, Wall W, Marotta P, Hernandez, Alejandro R. Liver Unit, London Health Science Centre, Canada Published in: Hepatology International in January 2011. *PMID*: 214841.
- Surgical Management of Biliary Complications following Living Donor Liver Transplantation. Hatem Khalaf, Khalil Alawi, Hamad Alsuhaibani, Bassem Hegab, Yasser Kamel, Ayman Azzam, Hamad Albahili, Mohammad Alsofayan, Mohammed Al Sebayel. *Clinical Transplantation* 2011 May; 25(3): 504-10.
- Treatment of genotype 4 hepatitis C recurring after liver transplantation using a combination of pegylated interferon alfa-2a and ribavirin. Al-Hamoudi W, Mohamed H, Abaalkhail F, Kamel Y, Al-Masri N, Alqahtani S, Al-Sofayan M, Khalaf H, Al-Sebayel M, Al-Jedai A, Abdo A. *Dig Dis Sci*. 2011 Jun; 56(6):1848-52.
- Liver transplantation in patients with hepatocellular carcinoma: a single-center experience. Ayman Azzam, Bassem Hegab, Hatem Khalaf, Hamad Albahili, Hazem Mohammed, Yasser Kamel, Faisal Abal khail, Waleed Al Hamoudi, Mohammad Alsofayan, Mohammed Alsebayel. *Exp Clin Transplant*. 2011 Oct; 5: 323-328.

ORAL PRESENTATIONS/INVITED SPEAKER

- Leberlebendspende beim HCC (Living Related Liver Transplant for HCC), 3. Interdisziplinares Symposium Primare Leberkarzinome, 19 February 2011, Berlin, Germany. Broering D.
- Surgery for Liver Metastases: How Far Should the Surgeon Go? International Saudi Colorectal Forum. 26-30 March 2011. King Faisal Specialist Hospital & Research Centre (Four Seasons Hotel), Riyadh, Saudi Arabia. Broering D.
- •"Actual Status of Pediatric Liver Transplantation, 3rd Pediatric Gastroenterology Gulf Group Forum. 30 March–01 April 2011. Abu Dhabi, United Arab Emirates. Broering D.

- Improving Outcomes in Pancreas Transplantation. 2nd Gulf Cooperation Council (GCC) Organ Transplantation Congress, 03-06 October 2011, Riyadh, Saudi Arabia. Broering D.
- Surgical Approach to Childhood Cancers. Childhood Cancer and Blood Disorders: Achievements and Challenges Symposium. 18-20 October 2011, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia. Broering D.
- Current Status of Hepatic Transplantation–Anatomical Basis for Liver Transplantation. 21st World Congress of the International Association of Surgeons, Gastorenterologists and Oncologists (IASGO 2011), 09-12 November 2011, Tokyo, Japan. Broering D.
- Surgical Experience in Pediatric Liver Transplant. Eastern Province International Pediatric Gastroenterology & Liver Transplant Conference, 30 November to 01 December 2011, Dammam, Saudi Arabia. Broering D.
- Immediate Complication Post Liver Transplantation. Eastern Province International Pediatric Gastroenterology & Liver Transplant Conference, 30 November–01 December 2011, Dammam, Saudi Arabia. Broering D.
- Impact of Prevalent Steatosis on the Living Donor Liver Transplant Program in Saudi Arabia: Analysis of 975 Living Related Liver Donors. Naglaa Allam, Mohammed Al Sofayan, Hatem Khalaf, Hamad Al Bahili, Yaser Medhat, Bassem Hegab, Hazem Mohammed, Khalil Alawi, Ayman Azzam, Hadil Al Manna, Faisal Aba Alkhail, Yasser Elsheikh, Mousa Faquih, Mohamed Neimatallah, Mohamed Faramawi, Ayman Abdo, Mohammed Al Sebayel, Waleed Al Hamoudi. Oral Presentation in: The 8th Pan-Arab Conference of Gastroenterology and the 11th Conference of the Saudi Gastroenterology Association 8-10 February, 2011.
- Liver Transplantation for Metabolic Disease: Ten-Year Experience. Naglaa Allam, Hatem Khalaf, Yasser Medhat, Hazem Mohamed, Hamad Al Bahili, Waleed Al Hamoudi, Faisal Aba Alkhail, Bassem Hegab, Ayman Azzam, Khalil Alawi, Mohammed Al Sofayan, Ayman Abdo, Mohammed Al Sebayel. Oral Presentation in: The 8th Pan-Arab Conference of Gastroenterology and the 11th Conference of the Saudi Gastroenterology Association 8-10 February, 2011.
- Revising the upper limits of normal for serum alanine aminotransferase in a Saudi Arabian population with normal liver histology. Waleed Al-Hamoudi, Yasser Kamel, Hazem Hasan, Naglla Allam, Mohammed Al Sofayan, Hatem Khalaf, Hamad Al Bahili, Nasser Al-Masri, Mohammed Al Sebayel, Ayman Abdo, Faisal Aba Alkhail. King Faisal Specialist Hospital & Research Centre, Liver Transplant . Submitted to EASL meeting Berlin March 3-April 11, 2011.
- Incentive Based Procurement System to Increase Cadaveric Organ Donation. Al Sebayel M. Accepted for Poster Presentation in the 2011 Joint International Congress of ILTS, ELITA, & LICAGE, 22-25 June 2011.
- Day of Surgery Rehection of Doors in Living Donor Liver Transplantation. Hegab Bassem, Azzam Ayman, Mohamed Hazem, Kamel Yasser, Al Bahili Hamad, Khalaf Hatem, Aba AlKhail Faisal, Al Hamoudi Waleed, Al Sofayan Mohammad, Al Sebayel Mohammed. Accepted for Oral Presentation in the 12th Congress of the Society of Transplantation in Seoul Koreas, 25-28 Sept. 2011.
- The Usefulness of Lapaoscopic Hernia Repair in the Management of Incisional Hernias Following Liver Transplantation. Hegab Bassem, Khalaf Hatem, Azzam Ayman, Al Sulaimani Abdullah, Bamehriz Fahad, Salem Abdelrahman, Al Sofayan Mohammad, Al Sebayel Mohammed. Accepted for Oral Presentation in the 12th Congess of the Society of Transplantation in Seoul Koreas, 25-28 Sept. 2011.

POSTER PRESENTATIONS

- Incentive Based Procurement System to Increase Cadaveric Organ Donation. Al Sebayel M. The Joint International Congress of ILTS, ELITA, & LICAGE, 22–25 June 2011.
- The use of Anti Hepatitis Core Liver Grafts: De Novo Hepatitis B Recurrence in Cadaveric Liver Transplant Recipients. Mohammed Al Sebayel, Faisal Aba Al Khail, Hamad Al Bahili,

Waleed Al Hamoudi, Yasser Kamel, Hazem Mohamed, Hussein El-Siesy, Nasser Al Masri, Mohammad Al Sofayan, Mahmoud Saleh. 2011 Joint International Congress of ILTS, Valencia, Spain 22–26 June 2011.

- Safety and efficacy of Yttrium-90 microspheres for the treatement of hepatocellular carcinoma: A Single Center Experience. Faisal Aba AlKhail, Mohammed Al Sebayel, Hamad Al Suhaibani, Yasser Kamel, Hatem Khalaf, Hamad Al Bahili, Ayman Abdo, Waleed Al Hamoudi. EASL 2011, Vienna, Austria.
- Liver Retransplantation: A Single Center Experience in Saudi Arabia. Hatem Khalaf, Waleed Al Hamoudi, Hamad Al Bahili, Bassem Hegab, Mahmoud Saleh, Yasser Kamel, Hazem Mohamed, Naglaa Allam, Faisal Aba Al Khail, Hussein El-Siesy, Nasser Al Masri, Mohammad AlSofayan, Mohammed AlSebayel. 2011 Joint International Congress of ILTS, Valencia, Spain.

ABSTRACTS

- Pegylated Interferon Alfa-2a and Ribavirin for the Treatment of Genotype-4 Recurrent Hepatitis C after Liver Transplantation. Al-Hamoudi W, Mohamed H, Abaalkhail F, Kamel Y, Al-Masri N, Alqahtani S, Al-Sofayan M, Khalaf H, Al-Sebayel M, Al-Jedai A, Abdo A. Oral Presentation in APASL Annual Meeting March 2010 in China. Published in *Digestive Disease Science* in January 2011. PMID: 21221800.
- Multi-disciplinary Approach in Treating HCC: KFSH&RC Experience. Al Sebayel MI. Japanese-KFSH&RC Oncology Seminar, 02 March 2011.
- Day of Surgery Rejection of Donors in Living Donor Liver Transplantation: is it Acceptable. Bassem Hegab, Ayman Azzam, Hazem Mohamed, Yasser Kamel, Hamad Al-bahli, Faisal Abal Khail, Waleed Al-hamoudi, Mohammed Al Sofayan, Mohammed Al Sebayel. King Faisal Specialist Hospital & Research Centre, Liver Transplant. Presented in: EASL Meeting Berlin March 3-April 11, 2011 Abstract Published in: Journal of Hepatology, April 2011.
- Safety and efficacy of Yttrium-90 microspheres for the treatment of hepatocellular carcinoma a single center experience. Faisal Aba Alkhail, Yasser Kamel, Hazem Hasan, Naglla Allam, Mohammed Al Sofayan, Hatem Khalaf, Hamad Al Bahili, Nasser Al-Masri, Mohammed Al Sebayel, Ayman Abdo, Waleed Al-Hamoudi. King Faisal Specialist Hospital & Research Centre, Liver Transplant. Published as Abstract in: Journal of Hepatology, April 2011.
- Updates in Liver Transplantation, 1st Taif Surgical Update Meeting. Al Sebayel M. 11 January 2011, Taif, Saudi Arabia.
- Revising the upper limits of normal for serum alanine aminotransferase in a Saudi Arabian population with normal liver histology. Waleed Al-Hamoudi, Yasser Kamel, Hazem Hasan, Naglla Allam, Mohammed Al Sofayan, Hatem Khalaf, Hamad Al Bahili, Nasser Al-Masri, Mohammed Al Sebayel, Ayman Abdo, Faisal Aba Alkhail. King Faisal Specialist Hospital & Research Centre, Liver Transplant . Submitted to EASL meeting Berlin March 3-April 11, 2011.
- Retrospective analysis of the causes of rejection of 975 potential donors for living related liver transplantation: Single Center. Waleed Al Hamoudi, Faisal Aba AlKhail. Submitted to AASLD Annual Meeting, San Francisco, USA.2011.
- Revising the upper limits of normal for serum alanine aminotransferase in a Middle Eastern population with normal liver histology. Waleed Al Hamoudi, Faisal Aba AlKhail. Submitted to AASLD Annual Meeting, San Francisco, USA, 2011.

RESEARCH PROJECTS

PROJECT TITLE: **Pan Arab Liver Transplant Registry**

RAC # 2071 022

INVESTIGATORS: *Mohammed Al Sebayel, MD*

PROJECT DESCRIPTION: A web-based Liver Transplantation registry was established to monitor Liver Transplantation activities in KFSH&RC and towards the Arab World to better follow-up and care for liver transplant patients. The project objectives include the following:

1. To obtain the frequency of liver transplantation activity in KFSH&RC (Phase I) followed by KSA (Phase II) and Arab Countries (Phase III).
2. To measure the extent and magnitude of the problem of end-stage liver disease necessitating liver transplantation in KSA and the Arab World.
3. To document the treatment and assessment of treatment Outcome.

STATUS: Ongoing since April 2007.

PROJECT TITLE: **The correlates of the Male Sexual Dysfunction in Liver Transplantation Patients and the Impact of Management**

RAC # 2091 016

INVESTIGATORS: *Mohammed Al Sebayel, MD, Hamad Al Bahili, MD*

PROJECT DESCRIPTION: This is a retrospective study looking at the sexual function before and after transplant through interview with transplant patients.

STATUS: For completion. A shared study with Dept. of Urology.

PROJECT TITLE: **An Open-label, Single-arm, Phase II Trial of the Combination of Trans-arterial Chemoembolization (TACE) and Sorafenib in non Metastatic Unresectable Hepatocellular Carcinoma (HCC)**

RAC # 2091 040

INVESTIGATORS: *Mohammed Al Sebayel, MD, Monther Kabbani, MD*

PROJECT DESCRIPTION: This is a study looking at the impact of molecular targeted therapy on the patient's survival who received chemoembolization as well as the detailed profile of this combination.

STATUS: Approved. Data collection was suspended. A shared study with King Faisal Cancer Center.

PROJECT TITLE: **Outcome of 16 Patients after Liver Transplantation for Wilson's Disease: Experience from KFSH&RC Riyadh**

RAC # 2120 137

INVESTIGATORS: *Faisal Aba Al Khail, MD*

PROJECT DESCRIPTION: This is a retrospective analysis of the outcome of liver transplantation for Wilson's Disease patients in our center.

STATUS: For completion. A shared study with Dept. of Medicine.

PROJECT TITLE: **Liver Transplantation in 16 Patients for Wilson's Disease: Single Centre from Saudi Arabia**

RAC # 2111 095

INVESTIGATORS: *Mohammed Al Sebayel, MD, Faisal Aba Al Khail, MD*

PROJECT DESCRIPTION: This is a retrospective analysis of the outcome of liver transplantation for Wilson 's disease patients in our center.

STATUS: Completed, A shared study with Deptartment of Medicine.

PROJECT TITLE: **Randomized, Open-Label, Non-inferiority Study of Micafungin versus Standard Care for the Prevention of Invasive Fungal Disease in High Risk Liver Transplant Recipients**

RAC # 2101 095

INVESTIGATORS: *Mohammed Al Sebayel, MD (PI) and Faisal Aba Al Khail*

PROJECT DESCRIPTION: Phase IIIb, multi-center, randomized 1:1, open label trial comparing antifungal prophylaxis with micafungin to 'standard care' in liver transplant recipients considered to be at high risk of invasive fungal infection.

STATUS: Suspended. This study is multicentric. The subject accrual is competitive. Unfortunately by the time the approval was granted from RAC and SFDA there were only handful of subjects because of

this delay. The study was suspended by the sponsor (Astellas).

ACADEMIC & TRAINING ACTIVITIES

Hepatobiliary Surgery Fellowship Training accepting international fellows

PROJECT TITLE: **Microsurgery Training using Rat Models**

RAC # 2082 003

INVESTIGATORS: *Mohammed Al Sebayel, MD*

PROJECT DESCRIPTION: Training for artery anastomosis in Rodents and training in stitching vascular structures and vascular anastomosis. Goals: Developing the skills in perfecting this technique (i.e. artery anastomosis, then practicing suturing anatomical structures in this animal model).

STATUS: Approved, Ongoing (every Saturday PM).

OTC–SECTION OF LUNG TRANSPLANT UNIT

ORAL PRESENTATIONS

- Adult Cystic Fibrosis Care. Dr. Imran Nizami. Cystic Fibrosis Worldwide Middle East Conference. 5–7 December 2011 Riyadh, Saudi Arabia.

ORGAN TRANSPLANT CENTER UPCOMING ACTIVITIES

- Organ Transplant Monthly Research Forum: Hospital wide collaborative research meeting to discuss project ideas, present ongoing projects and cooperate to facilitate research activities. Next meeting is on Wednesday, September 19, 2012, 11 a.m.
- The Saudi International Congress on New Frontiers in Organ Transplantation from 4–7 March 2013 at the Four Seasons Hotel.

ORTHOPEDICS SURGERY

ORTHOPEDICS SURGERY

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Anwar Al-Rabiah, MD
Khalid AlIsmail, MD
Samar Rabbani, MD
Mahbub Khan, MD
Thamer AlHussainan, MD
Gamal Al Tamimi, MD
Dalal Bubshait, MD
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Majdi Hashem, MD
Samir AlSayegh, MD
Abdulaziz AlHageri, MD
Wessal Al Homaied, MD
Najla Al Bedawi, MD
Ammar Qutub, MD
Yousef Tawfik Khoja, MD
Ibrahim AlShaygy, MD
Ali Al Dossari, MD
Fahad AlKhalaf, MD
Ahmed ALSaeed, MD
Mr. Burhan Dhar, C.P.O.
Mohammed Shoukri, PhD
Mr. Abdeloniem Aldalee
Hanan Al Ghammas, MPH

We have several ongoing clinical research projects designed to improve the diagnosis of Orthopedic conditions and to improve the management of musculoskeletal disorders. Our clinical research studies involve the application of new healing and surgical techniques for our Orthopedic patients.

The objectives of the Orthopedics Surgery Department are:

- To perform quality clinical researches.
- To improve the quality of clinical care by developing new analytical methods for evaluating medical treatments and applying these methods to innovate approaches to patient care.
- To promote advancement of health outcomes research in patients.
- To educate all levels of health care provides in health sciences research.
- To investigate and disseminate the health policy implications of our research findings.

Finally, our department will continue to develop a deeper understanding of the biology and biomechanics of the musculoskeletal system, and to apply this knowledge to the improvement of Orthopedic materials, implants, surgical instrumentation and surgical techniques, thereby improving the quality of care to Orthopedic patients world-wide.

ONGOING RESEARCH PROJECTS

PROJECT TITLE: **Long Term Treatment of Congenital Pseudoarthrosis of Tibia (CPT) and Intramedullary Fixation**

INVESTIGATORS: *Z. AlZayed, D. Bubshait, M. Hashem, G. AlTamimi, W. AlHomid, M. Shoukri, A. AlDalee, H. AlGhammas*

RAC # 209 1084

PROJECT TITLE: **Clinical and Radiological Outcome of Shoulder Sequalae of Birth Brachial Plexus Palsy (A Retrospective review of 13 cases)**

INVESTIGATORS: *N. Hamdi, D. Bubshait, M. AlShouli, A. AlHageri*

RAC # 209 1092

PROJECT TITLE: **Duration and Adherence to International Guidelines of Venous ThromboEmbolism (VTE) Prophylaxis after Major Orthopedics Surgery**

INVESTIGATORS: *I. Imran, S. Rabbani, H. AlGhammas*

RAC # 2101 023

PROJECT TITLE: **Developmental Dysplasia of the Hip Registry**

INVESTIGATORS: *Z. AlZayed, W. Wade, N. Hamdi, H. AlGhammas.*

RAC # 2101 099

PROJECT TITLE: **One Time Stable Below Knee Residual Limb in Pediatric Amputee (Case Report)**

INVESTIGATORS: *W. AlHomaied, B. Dhar, Z. AlZayed*

Pub # 2110 024

PROJECT TITLE: **The Effect of Pamidronate on Union Rate After Fractures and Osteotomies in Lower Limbs in Osteogenesis Imperfecta Patients**

INVESTIGATORS: *Z. AlZayed, A. AlHageri, H. AlGhammas*

RAC # 2101 079

PROJECT TITLE: **The Sequel of Low Bone Mineral Density (BMD) on Saudi Girls with Adolescent Idiopathic Scoliosis (AIS) and It's Relation to the Surgical Outcome**

INVESTIGATORS: *Z. AlZayed, N. Bedawi, H. AlGhammas*

RAC # 2111 026

PROJECT TITLE: **Morphologic Characteristics of the Acetabulum and Proximal Femur of Untreated Developmental Dislocated Hips in Adults**

INVESTIGATORS: *W. Wade, S. AlSayegh, K. AlIsmail, I. Imran, I. AlShaygy, H. AlGhammas*

RAC # 2111 031

PROJECT TITLE: **Effectiveness of Intravenous Pamidronate on Upper Limbs Function among Osteogenesis Imperfecta Patients, KFSH&RC Experience**

INVESTIGATORS: *W. AlHomaied, Z. AlZayed, H. AlGhammas*

RAC # 2111 041

PROJECT TITLE: **Platelets-Rich Plasma Potential Application in Osteoarthritis of the knee**

INVESTIGATORS: *M. AlYamani, A. Qutub, H. AlGhammas*

RAC # 2111 090

PROJECT TITLE: **Microsurgical Practice for Resident**

INVESTIGATORS: *N. Hamdi, G. AlTamimmi, A. AlDossari, A. AlSaeed*

RAC # 2112 033

PROJECT TITLE: **Platelets-Rich Plasma (PRP) Potential Applications in the Shoulder Tendons Injuries: A Prospective Study**

INVESTIGATORS: *M. AlYamani, N. Bin Dajim, Y. Khoja, M. Khan, H. AlGhammas*

RAC # 2121 051

PROJECT TITLE: **Management of Obstetrical Brachial Plexus Palsy: The KFSH&RC Experience**

INVESTIGATORS: *N. Hamdi, G. AlTamimmi, A. AlSaeed, A. AlDossari, H. AlGhammas*

RAC # 2121 054

PROJECT TITLE: **Complications of Vertical Expandable Prosthetic Titanium Rib (VEPTR) Implant in Different Types of Scoliosis and Thoracic Insufficiency Syndrome**

INVESTIGATORS: *Z. AlZayed, K. AlMamoun, K. AlHajan, H. AlGhammas*

RAC # 2120 090

PROJECT TITLE: **Children's Play Ground Safety in Saudi Arabia (A Literature Review)**

INVESTIGATORS: *Z. AlZayed, F. AlKhalaf*

PROJECT TITLE: **Anterior Cruciate Ligament (ACL) Study (Epidemiological Study)**

INVESTIGATOR: *M. AlYamani*

2011 ABSTRACTS

TITLE: Long Term Treatment of Congenital Pseudoarthrosis of Tibia (CPT) and intramedullary Fixation

AUTHORS: *Z. AlZayed, D. Bubshait, M. Hashem, G. AlTamimi, W. AlHomid, M. Shoukri, A. Aldalee, H. AlGhammas*

BACKGROUND: Congenital pseudoarthrosis of the tibia (CPT) is a rare disease, having an incidence of approximately 1 in 250,000 live births. It presents as an abnormal dysplastic tibial segment with anteriolateral bowing which is difficult to treat because of fractures that occur and heal with abnormal tissue rather than bony tissue. CPT also has a high association with neurofibromatosis (see Fig. 1).

Spontaneous union may occur in approximately 3% of CPT cases; however, there are usually residual deformities and a high incidence of refracture. Surgical treatment is needed in the vast majority of CPT cases and one of several surgical interventions can be used. The King Faisal Specialist Hospital and Research Centre (KFSH&RC) has traditionally opted to treat CPT patients with resection and intramedullary fixation.

MATERIALS AND METHODS: This is a retrospective study to assess the method of fixation used at the KFSH&RC, the fracture union rate, and the residual deformities of the affected leg.

We will review all the medical records, including medical charts and x-rays of all CPT cases treated at the KFSH&RC from 1985 to 2008. The research will focus on the type of fixation, union rate and type of residual deformities data. Classification of the results will be documented according to the Dr. Inan classification as excellent, good, fair and poor depending on the patient activity and residual deformity results.

RESULTS: The Medical Records of 16 patients with CPT, all of whom had undergone surgical treatment, were collected (12 boys [75%], 4 girls [25%]). The etiology was 9 with neurofibromatosis (60%). In 8 patients the right side was affected (50%); the left side was affected in the other 8 (50%). No bilateral involvement was noted. We had three different evaluators that reviewed the same medical record numbers for the 16 patients. And the data analysis results were slightly different between them because of the personnel subjectively differences.

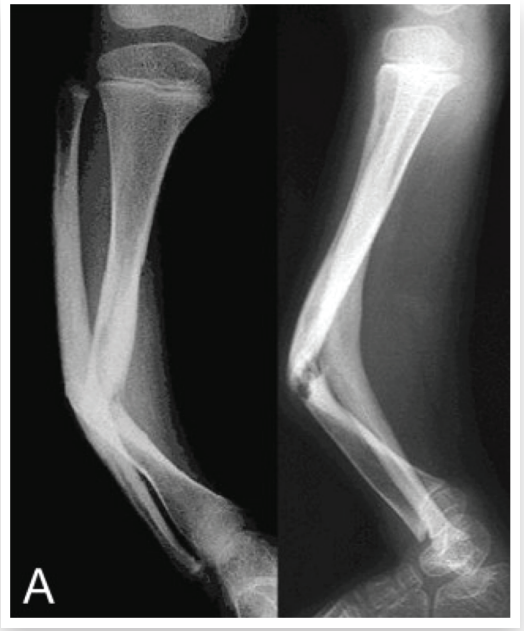

Fig 1. Congenital Pseudoarthrosis of the tibia (CPT) X-Ray

TITLE: Duration and Adherence to International Guidelines of Venous ThromboEmbolism (VTE) Prophylaxis after Major Orthopedics Surgery

AUTHORS: *I. Imran, S. Rabbani, H. AlGhammas*

BACKGROUND: The high risk of Venous Thromboembolism (VTE) among patients undergoing major lower limb surgery is well recognized. Recommendations for appropriate prophylaxis based on solid scientific evidence have been published by the American College of Chest Physicians (ACCP) on a regular basis since 1986. Similar guidelines have been developed by other expert groups. The guidelines from the American College of Chest Physicians recommend a minimum of 10 days of anticoagulant prophylaxis. In the past, anticoagulant prophylaxis was often given to the patient during his or her hospital stay but was discontinued on discharge.

As the VTE risk continues after hospital discharge, it will be interesting to investigate the compliance regarding anticoagulation treatment with VTE prophylaxis versus international guidelines in patients having undergone a major orthopedic surgery whatever the destination of the patient after hospital discharge. This study plans to collect information on the venous thromboembolism prophylaxis prescribed to patients after major orthopedic surgery in order to evaluate if the current guidelines are respected and to know the reasons why they might not be respected.

AIMS: The primary aim of our study is to compare real life VTE prophylaxis received by patients having undergone major orthopedic surgery versus international guidelines (ACCP 2008) during hospitalization. Then, we will also compare as a secondary aim the real life VTE prophylaxis prescribed to patients having undergone major orthopedic surgery versus international guidelines (ACCP 2008) after hospital discharge.

METHODS: This is a multicenter, longitudinal, non-interventional, observational study conducted within the Intercontinental region on the therapeutic strategy, to evaluate the actual duration of the prescription of venous thromboembolism prophylaxis after major orthopedic surgery compared to the international guidelines (ACCP 2008) for VTE prevention.

Results: 112 patients out of 120 planned have been recruited till now in a total of 8 centers all over the Kingdom of Saudi Arabia. In KFSH&RC, We recruit 30 patients.

TITLE: Developmental Dysplasia of the Hip Registry

AUTHORS: *Z. Alzayed, W. Wade, N. Hamdi, Thamer AlHussainan, H. AlGhammas*

BACKGROUND: Developmental dysplasia of the hip (DDH) has been recognized from the time of Hippocrates. It refers to a spectrum of anatomical abnormalities of the hip joint arising from a deviation in normal hip development during embryonic, fetal and infantile growth periods.

KFSH&RC receives yearly a large number of neglected cases referred from all over the kingdom; and some of them were maltreated in their local hospitals which results in poor functional outcome of some of these hips. Therefore; the rationale for developing this registry is to determine the magnitude of DDH cases encountered in our population. Additional centres will be collaborating with the registry.

The Aims of the DDH Registry are:

- To provide vital statistics and referral pattern about DDH prevalence and incidence in King Faisal Specialist Hospital & Research Centre (KFSH&RC) firstly. Then, Riyadh Hospitals at the second stage. And, Kingdom Hospitals in the final stage gradually.
- To identify the risk factors associated with DDH cases.
- To document the treatment procedures and to assess their outcomes.
- To establish a treatment protocol for the DDH cases.
- To create further studies and scientific researches in DDH field.
- To improve the patient care.
- To establish a national screening program target the high risk group.

POPULATION: All patients diagnosed with any of the DDH, receiving treatment or seeking medical attention or born with DDH at KFSH&RC will be registered.

REPORTS: Registry data will be reported annually. Registry reports will be sent to the investigators by the registrar through the chair of the Registry Committee. The Registry Committee will disseminate non-confidential data through annual reports. These reports include the routine compilation of rates, changing trends, and other findings and recommendations that are useful to public health officials and other scientists. The Registry will continue to refine its data collection and analysis methods in order to provide the most accurate information possible for public health policy, scientific research, and medical services.

TITLE: One Time Stable Below Knee Residual Limb in Pediatric Amputee (Case Report)

AUTHORS: *W. AlHomaied, B. Dhar , Z. AlZayed*

ABSTRACT: Appositional or terminal overgrowth of bone is common in children with an acquired or congenital amputation. This problem is seen primarily after amputation through the diaphysis of the tibia. Management of this condition requires frequent prosthetic adjustments or operative revision of the limb.

Fusion of the distal tibia and fibula in transtibial amputations was first described in the early 20th century by Janos Ertl in Hungary. The concept was later popularized in the United States by Col. Philip A. Deffer in the 1960s and multiple modifications of the original technique have since been described.

We concentrate on painless rounded functional residual limbs and end weight bearing capability. So, we use Ertl's procedure to evaluate the effect of this procedure on termination of overgrowth of bone in two children, one diagnosed as bilateral tibia hemimelia and the other as bilateral vascular insufficiency both underwent bilateral transtibial amputation following that technique. After reviewing the literature regarding that technique, our hospital is first in applying the modified Ertl's procedure in pediatric patients who need bilateral transtibial amputation due to pathological limbs.

CONCLUSION: The osteomyoplastic transtibial amputation or reconstruction in pediatric transtibial amputee with bilateral pathology, Modified Ertl's procedure (see Fig 2) is technically challenging with more operative time needed than conventional techniques, but it has a high success potential and high patient satisfaction by preventing bony overgrowth and its complication regarding pain, instability and prosthetic problems. Such amputations can lead to improved quality of life and thereby expand their horizon. We have therefore concluded that modified Ertl's procedure as one of the best solutions for transtibial amputation in children (see Fig 3).

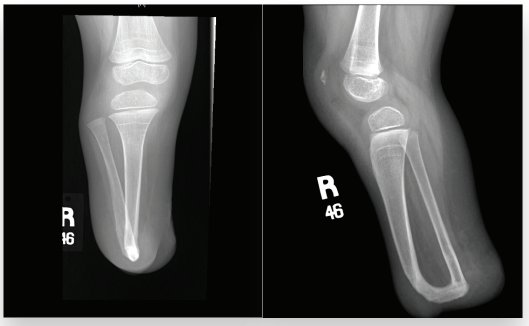

Fig 2. Show a PA and lateral views of a modified Ertl's procedure (transtibial amputation) of one of the patient showing a healed tibiofibular bony bridge.

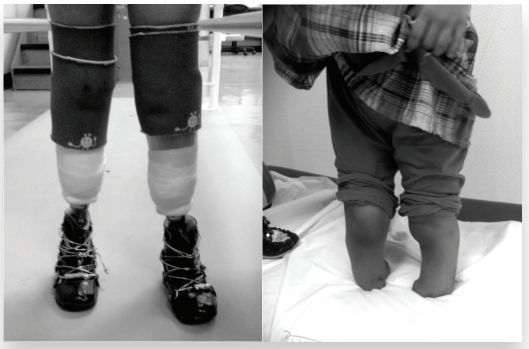

Fig 3. Show the first patient during standing with end weight bearing with and without wearing the prosthesis.

TITLE: **The Effect of Pamidronate on Union Rate after Fractures and Osteotomies in Lower Limbs in Osteogenesis Imperfecta Patients**

AUTHORS: *Z. AlZayed, A. AlHageri, H. AlGhammas*

BACKGROUND: Osteogenesis Imperfecta is an autosomal dominant disorder of collagen type 1. It leads to heterogeneous group of presentation including multiple fractures and deformities. The recommended medical treatment is Bisphosphonates, which helps in improving their pain and reduces fractures. Surgical osteotomies are indicated in severe bowing of the bones to improve their functional outcome and rehabilitation.

AIMS: The aim of this study is to evaluate the effect of Bisphosphonates on healing of fractures and osteotomies.

METHODS: This is a retrospective study of Osteogenesis Imperfecta patients who were treated in KFSH&RC from 1985 till 2009. And, we will concentrate on the union achievement results of fractures and osteotomies with patients who are treated with pamidronate (see Fig. 4).

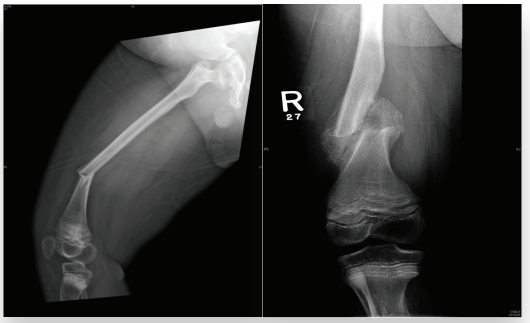

Fig 4. The fracture before and after with a patient who is treated by pamidronate.

RESULTS: Forty four patients (22 boys, 22 girls) with moderate to severe OI were included in this study. Age ranged from 5 to 27 years of age (mean 14.7 ±5.6). The surgical technique for fixation was chosen based on the type of fracture, presence of deformity, bone quality, and the characteristics of each patient. Theses techniques included the use of Rush intramedullary rods, and telescopic rods. The radiological parameters showed union achievement in 50 lower limbs.

TITLE: **The Sequel of Low Bone Mineral Density (BMD) on Saudi Girls with Adolescent Idiopathic Scoliosis (AIS) and Its Relation to the Surgical Outcome**

AUTHORS: *Z. AlZayed, N. Bedawi, H. AlGhammas*

BACKGROUND: Scoliosis is a three-dimensional (3D) structural spinal deformity characterized by both vertebral rotation and lateral curvature greater than 10° (see Fig. 5). Idiopathic scoliosis is the most common type of structural scoliosis. Generalized low bone mass has been well documented in patients with Adolescent Idiopathic Scoliosis (AIS).

MATERIALS AND METHODS: This is a retrospective study, which will review 50 Saudi girls with AIS aged from 8 to 16 years, who underwent posterior spinal fusion and instrumentation in the period from 2006 till 2009, with 1 year follow up. There will be review of patients' charts, for the preoperative clinical history and postoperative outcomes. Review of patients' preoperative MRI and DEXA scan.

AIMS: The aims of this study are to estimate the sequel of low BMD on Saudi girls with AIS, to identify patients at risk for complications prior to surgical intervention, and to assess the outcome of management among Saudi girls with AIS and low BMD.

RESULTS: The mean age of AIS (Adolescent Idiopathic Scoliosis) was 15.25±0.89. The mean weight was 46.23±6.9 while the mean height was 152.83±7.52. We found that the mean of Calcium level was 2.26±8.5 and the mean of Phosphorus level was 1.28±0.34. Additionaly, the mean of vitamin D was 16.6±14.6. Finally, the estimated blood loss mean was 543.7±247. Eight patients were involved in our study, and two of them had a BMD Z-score lower than the normal limits (< -1.00). There is a moderate correlation between the BMD and the vitamin D (r= -0.634, p=0.091). There is a weak correlation between the BMD and the blood loss (r= -0.173, p=0.682) although not significant.

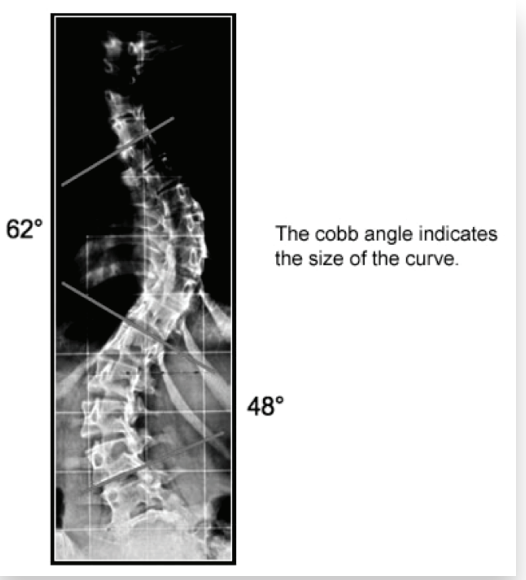

Fig 5. Adolescent Idiopathic Scoliosis X-Ray.

TITLE: **Morphologic Characteristics of the Acetabulum and Proximal Femur of Untreated Developmental Dislocated Hips in Adults**

AUTHOR: *W. Wade, S. AlSayegh, K. AlIsmail, I. Imran, I. AlShaygy, H. AlGhammas*

BACKGROUND: Developmental dysplasia of the hip (DDH) is a common orthopedic pathology in Saudi Arabia. A large number of these patients go undiagnosed or are left untreated and present in the 2nd to 4th decade of life with a painful established dislocated hip. Joint arthroplasty is the surgical solution for such patients. Total hip replacement in patients with an untreated developmental dislocated hip is surgically challenging, because of the distorted morphologic changes of the dysplastic hip and the lack of acetabulum bone volume. Preoperative knowledge of such bony changes will assist the surgeon in planning his surgical technique and preempt any surgical obstacles.

Untreated developmental dislocated hips seldom will be encountered in developed countries and therefore the acetabulum and proximal femur morphologic changes in adults with established dislocated hips have not previously effectively been studied.

METHODS: This is a retrospective study based on CT information of DDH patients who presented to the orthopedic clinic for treatment at KFSH&RC between 2005 and 2010 requiring total hip replacement procedures.

AIMS: The aim of this study is to evaluate and document the morphology changes of the acetabulum and proximal femur in untreated developmental dislocated hips in adult patients by means of 3D CT reconstruction (see Fig. 6).

RESULTS: We have collected the data for 16 hips of 12 patients. Three patients were excluded; two of them had a history of previous surgery and the third one had a traumatic dislocation. The study at present comprised 12 hips. The data emphasizes the unique configuration of this hip morphology.

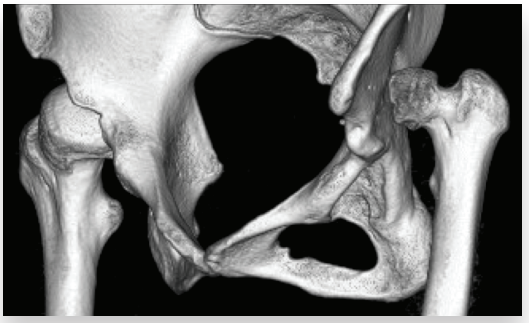

Fig 6. 3D CT of dislocated hip showing acetabulum shape and Morphology of femoral head.

TITLE: **Effectiveness of Intravenous Pamidronate on Upper Limbs Function among Osteogenesis Imperfecta Patients, KFSH&RC Experience**

AUTHOR: *W. AlHomaied, Z. AlZayed, H. AlGhammas*

ABSTRACT: Osteogenesis Imperfecta (OI) is mainly an autosomal dominant disorder of collagen type 1. It leads to heterogeneous group of presentation including multiple fractures and deformities. The recommended medical treatment is Bisphosphonates, which helps in improving their pain and reduces fractures as well as improves their function. The aim of this study is to evaluate the effect of Bisphosphonates on reduction of pain as well as to assess the improvement quality of patient's life.

METHODS: This is a prospective study of Osteogenesis Imperfecta patients who will be treated in KFSH&RC with Intravenous Pamidronate. We will concentrate on upper limb functional assessment (see Fig. 7), reduction of pain and improvement of quality of life.

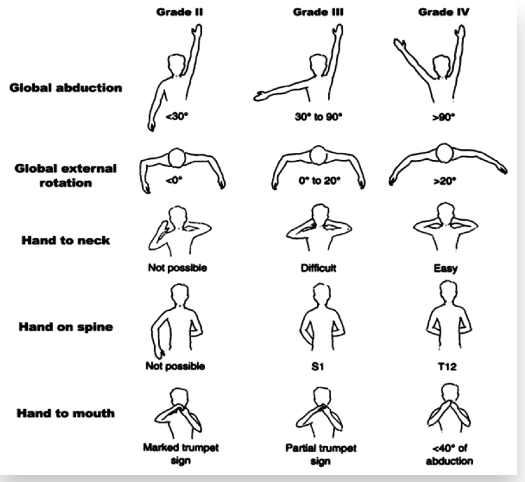

Fig 7. Modified mallet system to assess active shoulder movement.

TITLE: **Platelets-Rich Plasma Potential Application in Osteoarthritis of the Knee**

AUTHORS: *M. AlYamani, A. Qutub, H. AlGhammas*

BACKGROUND: Platelet-Rich-Plasma (PRP) use in tendon and ligament injuries has several potential advantages, including faster recovery and possibly a reduction in recurrence, with no adverse reactions described. However, only 3 randomized clinical trials have been conducted. Not only has PRP been used for tendons and ligaments but also it has been used and tested in Knee osteoarthritis. It was concluded in sequel of studies that "The positive trends and safety profile demonstrated could potentially be used to inspire a larger, blinded, and randomized clinical trial to determine whether platelet-rich-plasma is safe and effective for the treatment of knee osteoarthritis."

The safety of this study comes from the use of autologous PRP injections, which insures avoidance of body immunologic reactions. Only minor adverse events were detected, such as a mild pain reaction and effusion after the injection, which persisted for not more than 2 days. In one study there were no adverse reaction reported.

THE MAIN AIMS OF THE STUDY ARE:

1. To assess the effectiveness of autologous PRP injection in terms of pain and functional improvement.
2. To assess the possibility of PRP injection to act as an alternative to surgery in certain pathology: mild to moderate osteoarthritis.

MATERIAL AND METHODS: This is a prospective study to evaluate the effectiveness of autologous PRP injections in patients with mild to moderate osteoarthritis. All patients will be offered the participation in the study, consent will be explained to them and will be given four weeks to think and decide about their participation. Once the patient agrees, he/she will be evaluated then he/she will be received the first injection in the clinic (see Fig. 8). Reevaluation then will take place 4 weeks after first injection with possible second injection and 12 weeks after the first injection with possible third dose. Then, there is an every three months evaluation up to one year. The procedure takes from 30 to 45 minutes. The following measures are used to evaluate patients' condition and progression: X-rays, International Knee Documentation Committee (IKDC) subjective and objective score each time the patients come for evaluation.

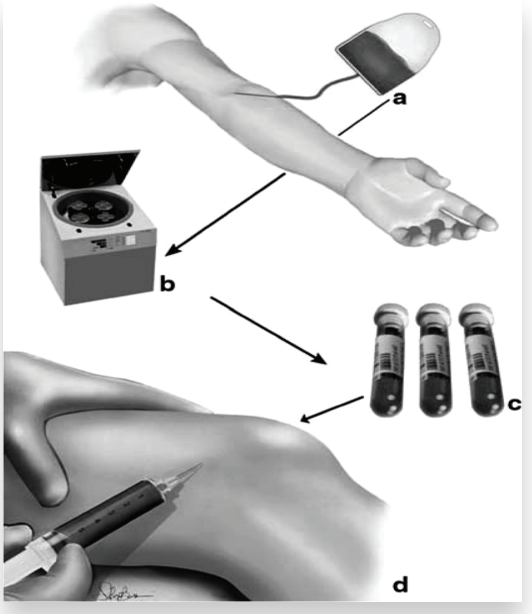

Fig 8. Blood samples are processed, 5ml PRP is obtained for intraarticular injection.

PATHOLOGY AND LABORATORY MEDICINE

CHAIRMAN

Fouad Al Dayel, MD, FRCPA, FRCPath

PATHOLOGY AND LABORATORY MEDICINE

RESEARCH ACTIVITIES

PROJECT TITLE: **Development of Human Embryonic Stem Cells (hESCs) Lines From Discarded IVF Laboratory Embryos, and Mouse Embryonic Stem Cells (mESCs) for the Treatment of Genetic Metabolic Disorders; A Major Cause of Disability in Children**

RAC # 2080 040

INVESTIGATORS: *Aida I Al Aqeel, Chaker N Adra, Serdar Coskun, Abdulkareem A. Alaiya, Mashael Al Deery*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: This project will focus on the generation of human embryonic stem cells (hESCs) lines from discarded IVF laboratory embryos, and mouse embryonic stem cells (mESCs). This will be explored for potential therapeutic option for various Genetic Metabolic Disorders, which are major causes of mental and developmental handicap in children. The project started for sample collection in January 2012.

PROJECT TITLE: **Preimplantation Genetic Diagnosis by Haplotyping (PGH) Using whole Genome Amplification**

RAC # 2081 061

INVESTIGATORS: *W. Qubbaj, Z. Al-Hassnan, S. Coskun, M. Al-Owain, M. Al-Sayed, Z. Rahbeeni, H. Banjar, K. Awartani, R. Al-Rejjal, S. Al-Hassan, M. Al-Deery, A. Bal-Obaid, A. Qari*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: This study aims to develop a preimplantation genetic haplotype (PGH) strategy on MDA products of single cells (blastomeres) for various type of diseases under the following conditions: (*i*) the disease mode of inheritance is known, (*ii*) the gene causes the disease is identified and it's location is mapped, (*iii*) a full family pedigree and accurate information is necessary, with an accesses for further investigations regarding the disease, to sort out the linkage analysis is required (accesses for affected individual within the family and other normal and carriers members if possible), (*iv*) sufficient markers should be tested and a number of informative markers at both the 5' and the 3' of the gene should be considered to rule out any risk of crossing over which might jeopardized the diagnosis. Approximately, 100 cycles were included into the study and it was found that PGH results are in concordance with mutation analysis and serves as assurances when the mutation results are inconclusive. PGH is now routinely applied to most of the PGD cases.

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

RAC # 2091 001

INVESTIGATORS: *Wafa Qubbaj, Serdar Coskun, Saad Al-Hassan, Meshael Al-Deery, Wesam Kurdi, Maha Tulbah, Zuhair Al-Hassnan, Mohammed Toulimat*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: This project is closed due to the lack of man power for experimental work. A revised proposal is now funded by KACST.

PROJECT TITLE: **Genomics and Transcriptomics Analysis of Ovarian Hyperstimulation Syndrome: An Integrated Molecular Look to a Complex Syndrome**

RAC # 2100 002

INVESTIGATORS: *Maha Dagestani (PI), Serdar Coskun, Mashael Al Deery, Dilek Colak, Khalid A. Awartani, Namik Kaya*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: This project involves in genome-wide gene expression profiling of the different stages of OHSS, genome-wide association analysis to find potentially important SNPs and Copy Number Variations (CNVs) causing susceptibility as risk factors. The project is at the stages of sample collection, experimentation and data analysis.

PROJECT TITLE: **The Use of DHEA in Poor Ovarian Responders-IVF Outcome**

RAC # 2111 079

INVESTIGATORS: *K. Awartani, R. Al-Rejjal, S. Al-Hassan, M. Al-Deery, S. Coskun, A. Al-Sanie, G. Ghurab*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: This is study approved by RAC, pending to start due to unavailability of the funds.

PROJECT TITLE: **Obstetrical and Neonatal Outcome After PGD: Eight Years Experience at KFSH&RC**

RAC # 2101 013

INVESTIGATORS: *Elham Al-Mardawi, Wafa Qubbaj, Serdar Coskun, Wesam Kurdi, Maha Tulbah, Samar Toukhi*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: This project is designed to determine if there is any observable effect of PGD on perinatal morbidity and mortality, birth defects, neonatal outcome, and to find the rate of misdiagnosis. First analysis by looking at 70 babies born following PGD showed similar outcome compared to natural conceptions. The data collection is ongoing to increase the number.

PROJECT TITLE: **Cell Free Fetal DNA (cffDNA) in maternal circulation; an alternative approach for non-invasive prenatal diagnosis (NIPD) along with the evaluation of a novel approach using Bead-based Emulsion PCR (BEAMing)**

Approved by National Strategic Grant Program for 1,812,000 SR under The Long-Term Comprehensive National Plan for Science, Technology and Innovation.

RAC # 2120 010

INVESTIGATORS: *Wafa Qubbaj, Bedri Karakas, Serdar Coskun, Saad Al-Hassan, Zuhair Al-Hassnan*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: The first aim to confirm PGD diagnosis in patients who get pregnant following PGD with informative haplotyping as a first step towards establishing NIPD in KFSH&RC 5 weeks after embryo transfer. A novel approach in NIPD and a highly sensitive technology that could detect fetal DNA in mother's blood between 2 to 4 weeks after embryo transfer will be evaluated. We will test the sensitivity and earliest detection limits of a non-invasive bead based emulsion PCR technology (BEAMing) using ccffDNA from mother's blood. This project is approved by KACST and pending the consent form approval to start.

PROJECT TITLE: **Helicobacter pylori Eradication with 14-day Standard Triple Therapy versus 10-day Sequential Therapy**

RAC # 2111 019

INVESTIGATORS: *Fahad Al Sohaibani, Hamad Alashgar, Mohammed Alfadda, Khalid AlKhatani, Ingar Kagevi, Mohammed Khan, Sahar Althawadi*

PROJECT DESCRIPTION: To determine if the sequential therapy is superior to the standard 14-day triple therapy for the eradication of *H. pylori* in adults and the study will be to test the susceptibility of *H. Pylori* to the antimicrobials amoxicillin, metronidazole, tetracycline, ciprofloxacin, levofloxacin and clarithromycin.

PROGRESS, MAJOR FINDINGS: Data collection in progress.

PROJECT TITLE: **Microbiology of Airway Disease in Children with Cystic Fibrosis at King Faisal Specialist Hospital and Research Centre**

INVESTIGATORS: *Sami Alhaider, Hanna Banjar, Ibrahim Al-Mogarri, Sahar AlThawadi*

PROJECT DESCRIPTION: This study will provide national data on microbiology of respiratory infections for patients with CF. Information will help understanding special characteristics of CF disease in Saudi Arabia and hopefully to improve care delivered to CF patients.

PROGRESS: in-process.

PEDIATRIC ONCOLOGY

PEDIATRIC HEMATOLOGY ONCOLOGY

CHAIRPERSON
Amani Al-Kofide, MD

DEPUTY CHAIRMAN
Asim Belgaumi, MD

CENTRAL DATA UNIT
Dr. Asim Belgaumi, *Director, CDU*
Khawar Saeed Siddiqui, *Head*
Mohammed Viqaruddin
Grace Barria
Syed Ali Jafri
John Paul Sahibbil
Hanan Al Ghammas, MPH

ADMIN SUPPORT
Marilou Carido
Gerlia Repia Bau
Leah Abad
Christine Lu
Manny Quindo

CLINICAL RESEARCH

The Central Data Unit (CDU) has prioritised the prospective collection of patients care related data and research data for RAC-Approved studies. PI's are being encouraged to obtain grant-support for collection of retrospective data or collect the data themselves. Collection of prospective data is progressing well and this practice has resulted in increased number of research projects and abstracts/publications.

Three (3) New clinical research studies were approved by RAC in 2011 with Department members as investigators

ABSTRACTS/PRESENTATIONS (ORAL&POSTER)/MANUSCRIPTS

In 2011 the Department had 18 abstracts and presentations (both oral and poster) and 10 full-length manuscripts published. Four book chapters and one scholarly article were also contributed by the Department members. This is a significant improvement compared to the previous 5 years. List of abstracts and publications for the year 2011 is also provided.

LABORATORY RESEARCH

The Department continues to collaborate with the Research Centre at KFNCCC in Translational Research.

DEPARTMENT RESEARCH COMMITTEE

This committee continues to critically scrutinize the scientific & research merits of new proposals before submission to ORA.

RESEARCH INFORMATION EXCHANGE

In order to continuously update members of the department on Research Activities in the department there are two fora the "CDU Minute" at each Department Meeting and the Research Activities Meeting (RAM) held quarterly. The latter also acts as a platform for presentation of Research in the Concept Phase.

RAC-APPROVED RESEARCH ACTIVITY

PROJECT TITLE: **Underlying Genetics Of Familial Hemophagocytic Lymphohistiocytosis (Flh) In Saudi Arabia**

RAC # 2080 041

INVESTIGATORS:–*Ali Al Ahmari (PI), Osama Alsmadi (PI), Ibrahim Al-Fawaz, Mouhab Ayas, Bandar Al Saud*

PROJECT TITLE: **Allogeneic Stem Cell Transplant Using Reduced Intensity Conditioning—A Pilot Study**

RAC # 2081 053

INVESTIGATORS: *Mouhab Ayas (PI), Abdlh Al-Jefri, Amal Al-Seraihy, Ali Al Ahmari, Mohd Al-Mahr, Ashraf Khairy, Samer Markiz, Ibrahim Al Hassan, Hassan El-Solh*

PROJECT TITLE: **Cardiac Iron Overload And Efficacy Of Deferasirox Exjade On Patients On Chronic Blood Transfusion Secondary To Herediatary Blood Disorders, KFSH&RC**

RAC # 2081 106

INVESTIGATORS: *Abdlh Al-Jefri (PI), Abdulrahman Al-Musa, Nicy Joseph, Kwesi Sackey , Mohammad Salim, Rajeh Sabbah, Fahad Al Moharib, Mahasen Saleh, Yusuf Alkadh, Rubina Jamil Malik, Mahmoud Abu-Riash, Rajeev Sathiapalan, Mohammad Al Ghamdi*

PROJECT TITLE: **International Pediatric Fungal Network Registry**

RAC # 2091 044

INVESTIGATORS: *Ibrahim Bin Hussein, Asim Belgaumi*

PROJECT TITLE: **Second Allogeneic Sct In Pediatric Patients At KFSH&RC**

RAC # 2081 098

INVESTIGATORS: *Mouhab Ayas (PI), Abdlh Al-Jefri, Amal Al-Seraihy, Ali Al Ahmari, Mohd Al-Mahr, Ashraf Radwan, Samir Markiz, Hassan El-Solh*

PROJECT TITLE: **Allogeneic Bone Marrow Transplant In Children With Myelodysplastic Syndrome: KFSH&RC Experience**

RAC # 2081 046

INVESTIGATOR: *Amal Al-Seraihy*

PROJECT TITLE: **Allogeneic Stem Cell Transplant For JMML: Single Institution Experience**

RAC # 2071 048

INVESTIGATORS: *Ali Al Ahmari (PI), Othman Mosleh (PI), Mouhab Ayas, Ibrahim El-Hassan, Abdlh Al-Jefri, Amal Al-Seraihy, Mohd Al-Mahr, Samira Rifai, Ashraf Radwan, Samir Markiz, Hassan El-Solh*

PROJECT TITLE: **Allogeneic Stem Cell Transplantation In Patients With Fanconi Anemia Using Further Reduced Doses Of Cyclophosphamide With Addition Of Fludarabine**

RAC # 2071 037

INVESTIGATORS: *Mouhab Ayas (PI), Ali Al-Ahmari Ashraf Radwan, Abdullah Al Jefri Samir Markiz, Amal Al Seraihy Al-Hassan, Mohammad Al Mahr Hassan El Solh, Samira Rifai*

PROJECT TITLE: **Where Do We Stand With Chronic Immune Thrombocytopenia In Children? A KFSH&RC-Riyadh Experience**

RAC # 2071 012

INVESTIGATORS: *Rajeev Sathiapalan (PI), Abdlh Al-Jefri, Abdulrahman Al-Musa, Mahasen Saleh, Amal Al-Seraihy, Rajeh Sabbah, Nicy Joseph, Rubina Jamil Malik, Arlene Maculangan, Pranesh Kumar*

PROJECT TITLE: **Chemoreduction In Retinoblastoma**

RAC # 2061 040

INVESTIGATORS: *Amani Al-Kofide (PI), Saleh Mesfer, Khawar Siddiqui, Gamal El Din Hassan Mohamed, Yasser Khafaga, Ashraf Alrawashdeh*

PROJECT TITLE: **Retrospective Review Of Pediatric Ewing's Sarcoma (ES) And Primitive Neuroectodermal Tumor (PNET) Treated With The POG CCG At KFSH&RC 1995–2004**

RAC # 2051 015

INVESTIGATORS: *Ibrahim Al-Fawaz (PI), Mouhab Ayas Mohammed Al Shabanah, Samira Rifai Leifan Al Otaibi, Christopher Alviedo Abdulmoneim Eldali, Yasser Khafaga, Zakaria Habib*

PROJECT TITLE: **Prospective Evaluation Of Risk-Adapted Therapy For Pediatric Patients With Non-Lymphoblastic Non-Hodgkins Lymphoma**

RAC # 2051 018

INVESTIGATORS: *Asim Belgaumi (PI), Amani Al-Kofide Khawar Siddiqui, Rajeh Sabbah Mohammed Anwaruddin Iqbal, Yasser Khafaga Layla Osman, Ravichandran Kandasamy Qassim Al Harbi, Walid Aly Mourad Ashraf Alrawashdeh*

PROJECT TITLE: **Immune Reconstitution In Pediatric Patients Undergoing Allogeneic And Autologous SCT. A Single Institution Experience At KFSH&RC**

RAC # 2051 005

INVESTIGATORS: *Abdlh Al-Jefri, F. Al Mohareb, Y. Al Kadhi*

PROJECT TITLE: **GVHD in SCT Cases**

RAC # 2051 008

INVESTIGATORS: *Mouhab Ayas (PI),*

PROJECT TITLE: **Treatment Of Infentile Acute Leukemia With High Dose Chemotherapy Followed By HLA Matched Stem Cell Transplantation**

RAC # 2041 045

INVESTIGATORS: *Ashraf Radwan, Mouhab Ayas*

PROJECT TITLE: **Feasibility Of GCSF Stimulating Bone Marrow From Pediatric Donors As A Stem Cell Source For Allo BMT**

RAC # 2041 031

INVESTIGATORS: *Mouhab Ayas, Ashraf Radwan, Amal Al-Seraihy Mohammad Al Mahr, Abdlh Al-Jefri A. Iqbal, Samira Rifai, Hassan El-Solh*

PROJECT TITLE: **An Open-Label, Multicenter Trial On Efficacy And Safety Of Long Term Treatment With ICL 670 (10-20 mg/kg/day) In Beta Thalassemia Patients With Transfusional Hemosiderosis**

RAC # 2041 038

INVESTIGATORS: *Mouhab Ayas*

PROJECT TITLE: **Retrospective Review Of Pediatric Patients Diagnosed With Hodgkin Lymphoma Treated At KFSH&RC**

RAC # 2041 046

INVESTIGATORS: *Asim Belgaumi, Rajeh Sabbah, Khawla Sami Al-Kuraya, Amani Al-Kofide, Nicy Joseph, Rubina Jamil Malik, Walid Aly Mourad, Yasser Khafaja*

PROJECT TITLE: **A Prospective Study Of Invasive Fungal Infections Among Pediatric Patients 0–14 Years Of Age With Hematological Malignancies At KFSH&RC & KFNCCC&R**

RAC # 2041 006

INVESTIGATORS: *Rajeev Sathiapalan, Rong Bu, Ibrahim Bin Hussein, Asim Belgaumi Ali Al-Ahmari, Raghad Al-Saad Kishor Bhatia, Mohammad Qutub, Faisal Al Kurdi, Edna Al Moovar*

PROJECT TITLE: **PCR Assay For Detection & Quantification Of Fungal Infections In Pediatric Patients With Acute Leukemia & Myelodysplastic Syndrome**

RAC # 2021 054

INVESTIGATORS: *Ibrahim Bin Hussein, Hasan Shahin, Asim Belgaumi, Ali Al Ahmari Hussein Bagalb, Mouhab Ayas Edna Almodavar, Amal Al-Seraihy Zakaria Habib, Rajeev Sathiapalan Sami Hajjar, Saher Thawadi, Akram Tabassum*

PROJECT TITLE: **The Outcome Of Patients With Hlh Treated With Immuno-Chemotherapy Followed By SCT: A Single Centre Experience**

RAC # 2081 052

INVESTIGATORS: *Ali Al Ahmari, Mouhab Ayas, Abdlh Al Jefri, Amal Alseraihy, Ibrahim Al Fawaz, Mahasen Saleh, Hassan El Solh*

PROJECT TITLE: **The Outcome Of Children With Constitutional Single Cytopenia Post Allogeneic STC From Matched Related Donor: Single Centre Experience**

RAC # 2071 049

INVESTIGATORS: *Ali Al Ahmari, Ashraf Radwan, Mouhab Ayas, Abdullah Al Jefri, Amal Al Seraihy, Mohammad Al Mahr, Samira Rifai, Hasan El Solh*

PROJECT TITLE: **The Outcome Of Children With Aml Post Post Allogeinic Sct - Comparison Between Two Conditioning Regimens**

RAC # 2061 079

INVESTIGATORS: *Mouhab Ayas, Abdlh Al-Jefri, Amal Al-Seraihy, Asim Belgaumi, Ali Al Ahmari, Mohd Al-Mahr, Samira Rifai, Ashraf Radwan, Hassan El-Solh*

PROJECT TITLE: **HSCT In Children With Griscelli Syndrome**

RAC # 2081 044

INVESTIGATORS: *Ali Al Ahmari, Mouhab Ayas, Al Mousa, Al Saud, Amal Al Seraihy, Al Mohsen, Mohammad Al Mahr, H Al-Dekhi, Hassan El Solh*

PROJECT TITLE: **Langerhans Histiocytosis In Paediatric Patients At KFSH**

RAC # 2091 036

INVESTIGATORS: *Mouhab Ayas*

PROJECT TITLE: **A Local Survey On The Use Of Complementary And Alternative Medicine Among Pediatric Oncology Patients In Saudi Arabia**

RAC # 2091 047

INVESTIGATORS: *Amani Al-Kofide*

PROJECT TITLE: **Patterns Of Mortality Among Pediatric Patients With Cancer - A Review Of 5 Years Data (2005–2009)**

RAC # 2101 052

INVESTIGATORS: *Asim Belgaumi, Afshan Ali, Amani Al-Kofide, Khawar Siddiqui, Sophia Sahibbil, Amal Al-Seraihy, Samer Markiz*

PROJECT TITLE: **Related Haploidentical T-Cell Depleted Stem Cell Transplantation In Patients With Fanconi Anemia Lacking Matched Related Donors**

RAC # 2101 048

INVESTIGATORS: *Mouhab Ayas, Ashraf Radwan*

PROJECT TITLE: **Acute Infant Leukemias; Clinical Characteristics And Outcomes**

RAC # 2101 046

INVESTIGATORS: *Amal Al-Seraihy, Ashraf Radwan, Ali Al Shehri, Tarek Owaidah, Asim Belgaumi*

PROJECT TITLE: **Epidemiology Of Pediatric Cancer Referral And Outcome - A Review Of Five Years Data (2005–2009)**

RAC # 210 057

INVESTIGATORS: *Asim Belgaumi, Khawar Siddiqui, Ibrahim Al-Fawaz, Mohammad Al-Mahr, Mary Grace Barria, Amani Al-Kofide, Amal Al-Seraihy, Ghulam Pathan*

PROJECT TITLE: **Retrospective Analysis Of The Outcome Of Pediatric Patients Undergoing Allogenic Stem Cell Transplantation From Related Donors With A Class 1 Single Locus Antigen Mismatch**

RAC # 211 029

INVESTIGATORS: *Mouhab Ayas, Amal Al Seraihy, Abdullah Al Jefri, Ali Al Ahmari, Khawar Siddiqi, Ashraf Radwan, Hasan Shahin, Samer Markiz, Hassan El Solh*

PROJECT TITLE: **Retrospective Review Of The Outcome Of Salvage Therapy For Pediatric Patients Diagnosed With Acute Leukemia**

RAC # 211 073

INVESTIGATORS: *Asim Belgaumi, Asem Bukhari, Hassan El-Solh, Hazem Mahmoud, Amal Al-Seraihy, Abdulrahman Al-Musa, Ali Al-Ahmari, Mohammed Viqarrudin*

PROJECT TITLE: **Atypical Teratoid/Rhabdoid Tumors Of Central Nervous System; Experience From Saudi Arabia**

RAC # 211 074

INVESTIGATORS: *Essam Al Shail, Amani Al-Kofide, Khawar Siddiqui*

PROJECT TITLE: **Allogenic Stem Cell Transplantation in Patients with Fanconi Anemia: The KFSH&RC Experience**

RAC # 2061 037

INVESTIGATORS: *Mouhab Ayas, et. al.*

ABSTRACTS / PRESENTATIONS (POSTERS & ORAL)

1ST QUARTER (JANUARY, FEBRUARY AND MARCH)

- Asim Belgaumi, Rong Bu, Azhar Hussain, Khadija AS Al-Obaisi K, Mohammed Al-Mahr, Shahab Uddin, Khawla S Al-Kuraya. Real-time RT-PCR of Terminal Deoxynucleotidyl transferasev(TdT) is a useful tool for identification of Minimal Leukemia in Cerebrospinal Fluid. (Abstract accepted for presentation in a poster session in ACCR 102nd Annual meeting 2011 in Orlando, FL).

2ND QUARTER (APRIL, MAY AND JUNE)

- Ibrahim Al-Fawaz, Afshan Ali, Mouhab Ayas, Amani Al Kofide, Mary Grace Barria and Khawar Siddiqui. Treatment Outcome of Non-Rhabdomyosarcoma Soft Tissue Sarcomas (NRSTS) in Children of Saudi Arabia (Abstract accepted for poster presentation in 43rd SIOP Congress, Auckland, New Zealand, Oct 2011).
- Ibrahim Al-Fawaz, Mouhab Ayas, Afshan Ali, Amani Al-Kofide, Khawar Siddiqui, Samir Markiz, Kawther Salamah, Zakaria Habib and Yasser Khafaga. Treatment Outcome of Children with Low Stage Neuroblastoma (NBL) Experience from Saudi Arabia.(Abstract accepted for poster presentation in 43rd SIOP Congress, Auckland, New Zealand, Oct 2011).
- Mouhab Ayas, Ibrahim Al-Fawaz, Amani Al-Kofide, Afshan Ali, Taghreed Salman and Khawar Siddiqui. Langerhans Histiocytosis in Children of Saudi Arabia. (Abstract accepted for poster presentation in 43rd SIOP Congress, Auckland, New Zealand, Oct 2011).
- Ali Al-Ahmari, Mohammed Al-Hinai, Khawar Siddiqui, Mouhab Ayas, Amal Al-Seraihy,

Abdullah Al-Jefri and Hassan El-Solh. Outcome of Allogeneic Stem Cell transplantation in Children with Juvenile Myelomonocytic Leukemia. (Abstract accepted for poster presentation in 43rd SIOP Congress, Auckland, New Zealand, October 2011).

3RD QUARTER (JULY, AUGUST AND SEPTEMBER)

- Mouhab Ayas, Khawar Siddiqui, Amal Al-Seraihi, Ashraf Khairi, Abdallah Al-Jefri, Mohamad Al-Hinai, Asim Belgaumi, Ali Al-Ahmari, Hassan El-Solh. Risk factors for Acute Graft –Versus Host Disease after Related Hematopoietic Cell Transplantation in Children with Acute Leukemia (Abstract accepted for poster presentation at 2011 Annual Meeting of the American Society of Hematology in San Diego, California)

4TH QUARTER (OCTOBER, NOVEMBER AND DECEMBER)

- Mouhab Ayas, Asim Belgaumi, Amal Al-Seraihy, Abdullah Al-Jefri, Ali Al-Ahmari, Mohammed Al-Mahr, Ashraf Khairy, Samer Markiz, Hassan El-Solh. Outcome of Allogeneic Stem Cell Transplantation in Pediatric Patients with Acute Myeloid Leukemia after Conditioning with Busulfan, Cyclophosphamide, and Etoposide. (Abstract for 43rd SIOP Congress, Auckland, New Zealand, and Oct 2011).
- Mouhab Ayas, Amal Alseraihy, Hassan El-Solh, Abdullah Al-Jefri, Ali Al- Ahmari, Asim F Belgaumi, and Maher Albitar. Cytogenetic Risk Remains a Major Predictor of Outcome in Pediatric AML and ALL Treated with Allogeneic Stem Cell Transplantation. (Accepted in *ASH* December 2011).
- Amal Alseraihy, Mouhab Ayas, Abdullah Al-Jefri, Ali Al-Ahmari, Asim F Belgaumi, Claudia Ulrike Walter, Randa Nounou, Salem Khalil, Nasir Bakshi, Tarek Owaidah, and Hassan El-Solh. CD64 Expression Is An Independent Adverse Prognostic Factor in Pediatric Acute Myeloid Leukemia Treated with Allogeneic Stem Cell Transplantation. (Accepted in *ASH* December 2011).
- Hala Abalkhail, Amal Alseraihy, Mouhab Ayas, Abdullah Al-Jefri, Ali Al-Ahmari, Asim F Belgaumi, Claudia Ulrike Walter, Naeem A. Chaudhri, Fahed Almhareb, Hassan El-Solh, and Maher Albitar. Chimerism Analysis of Free Circulating DNA in the Prediction of Relapse in Patients with Acute Leukemia Treated with Stem Cell Transplantation. (Accepted in *ASH* December 2011).
- Amal Alseraihy, Mouhab Ayas, Abdullah Al-Jefri, Ali Al-Ahmari, Asim F Belgaumi, Claudia Ulrike Walter, Randa Nounou, Salem Khalil, Nasir Bakshi, Tarek Owaidah, and Hassan El-Solh. CD11b Expression Is An Independent Adverse Prognostic Factor in Pediatric Acute Myeloid Leukemia Treated with Allogeneic Stem Cell Transplantation. (Accepted in *ASH* December 2011).
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UROLOGY

UROLOGY

CHAIRMAN
Waleed Al Khudair, MD, FRCSC

The department of urology aims to have numerous substantial research projects. There are several on going projects concerning bladder cancer, prostatic cancer, congenital anomalies and female urology. In addition, we have had a hands-on workshop for training of Residents on Laparoscopic surgery and was successfully conducted in December 2011. A Microscopic surgery project is on-going for training of residents.

The department will continually aim to a successful future research endeavors.

RESEARCH ACTIVITY

PROJECT TITLE: **Detection of Incidental Prostatic Adenocarcinoma in Radical Cystoprostatectomy Specimens**

RAC # 2101 003

INVESTIGATORS: *Dr. Mohammed Al Otaibi (PI), Dr. Alaa Mokhtar Hammad, Dr. Asma Tulba, Hatem Khoja, Prof. Waleed Al Khudair, MD*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: All male patients undergoing radical cystoprostatectomy for carcinoma of the bladder will be prospectively selected. In this operation, the urinary bladder and the prostate are routinely removed. The prostate in the specimen will be sectioned separately and histopathologically examined by the pathologists for the presence of prostate cancer.

The Research Ethics Committee (REC) has accepted the revised Consent form on 31 October 2010 and recommended for approval.

A progress report is underway and for submission to the Office of the Research Affairs (ORA).

PROJECT TITLE: **Long Term Outcomes of Superficial Bladder Cancer: Patient Compliance for Follow-up and Oncological Outcome**

RAC # 2101 082

b)Investigators (as approved by the RAC)

INVESTIGATORS: *Prof. Waleed Al Khudair, MD, Dr. Alaa Moukhtar Hammad*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: To evaluate our follow up protocols at King Faisal Specialist Hospital & Research Centre for patients with superficial bladder cancer and assess the patient compliance to this protocol. Assessment of long term outcomes and impact of the first cystoscopy at 3 months on the prognosis and long term outcome of the disease progression and recurrence.

In compliance with the recommendation of the REC and CRC, the data collection form was submitted on 18 October 2010 and reviewed by the Clinical Research Committee (CRC) and the Research Ethics Committee (REC). Both committees accepted the reply conditionally provided the patients' identifiable information in the data collection form is replaced with code numbers. Data collection is underway.

PROJECT TITLE: **Project title and RAC No."Genomic and Proteomic Signatures of Prostate Cancer in Middle Eastern and North African (MENA) Populations**

RAC # 2091 099

INVESTIGATORS: *Dr. Mohammed Al Otaibi(PI), Dr. Raouf Seyam,*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: Patients presenting to the Urology department and identified to have high prostatic specific antigen are subjected to transrectal prostatic biopsy as routine management. Blood samples from 160 consecutive patients and the biopsy samples are frozen. Blood samples from 160 volunteers are used as controls. A urine sample will be collected form each participant and stored refrigerated. Participating subjects who do not have prostatic disease or family history of prostatic cancer will undergo urine sample collection and withdrawal of a blood sample only. All the blood and tissue samples are send to Cornell University, Quarter Genetic Department for genetic and proteomic studies. All the samples will be analyzed for genetic content and comparison will be carried out between healthy individuals and patients. These samples will be used only for this study and will be discarded after termination of the study. At the end of the study, it is anticipated that the molecular and genetic factors underlying the development of prostatic carcinoma in Saudi men will be identified and compared to published data in the industrialized world.

A progress report is underway to be submitted to ORA for continuing approval.

There has been no patient recruited into this project however, the project remains active.

PROJECT TITLE: **Project title and RAC No."Laparoscopic Nephrectomy: A single Institutional of Peri Operative and Follow up Outcomes**

RAC # 2101 005

INVESTIGATORS: *Dr. Mohammed Al Otaibi (PI), Prof. Waleed Al Khudair, MD, Dr. Hassan Al Zahrani, Dr. Naif Al Hathal*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: To review KFSH experience in Laparosocopic Nephrectomy pertaining to perioperative and follow-up results.

The Clinical Research Committee (CRC) has accepted the revised proposal provided that submission of a revised Case Report Form (CRF) that satisfactorily fulfills the requirements of the study. Also, the Committee suggested that the principal investigator should seek the assistance of the biostatistician in designing the appropriate CRF for the study.

An amendment to include a statistician is underway.

PROJECT TITLE: **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 # 2111 020

INVESTIGATORS: *Dr. Hassan Al Zahrani (PI), Dr. Abdullah Ghazi*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: The study will review the experience of a single surgeon at KFSH&RC providing homogeneous cohort of cases and avoiding the variation that different surgeons may approach suspected bladder perforation and their management.

The Clinical Research Committee (CRC) has recommended the approval of the proposal. However, the Research Ethics Committee (REC) has recommended the reply for approval provided the patient's identifiable information in the data collection form is replaced with code numbers.

Both Drs. Zahrani and Ghazi left the Hospital. An amendment to include Dr. Al Otaibi and Dr. Al Khudair as principal investigator is underway.

PROJECT TITLE: **Project title and RAC No."The Outcome of Robot Assisted Pyeloplasty for Pelviureteric Junction Obstruction in Adult Patients**

RAC # 2111 007

INVESTIGATORS: *Dr. Hassan Al Zahrani (PI), Dr. Ahmad Alenezi, Dr. Mohammed Al Otaibi, Dr. Khalid Al Othman, Prof. Waleed Al Khudair, MD*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: A retrospective study to review all cases of robot assisted pyeloplasty done at KFSH&RC over the last 5 years. The demographic, clinical, laboratory, imaging, operative, post operative and outcome factors will be analyzed.

The Committees have recommended the approval of the proposal and requested to provide a reply on the following concerns. The Department of Urology submitted a reply such as:

1. The expected number of Medical Records to be reviewed will be 45.
2. The timeline will be two (2) years and the role of the investigators are the following: writing manuscripts, data collection and data analysis.
3. Data collection sheet will be replaced by code numbers.

Both committees have accepted the department's reply and recommended the proposal – the waiver of informed consent and the revised data collection form for approval.

Dr. Hassan Al Zahrani has already left the Hospital. A memo for an amendment to replace the principal investigator is underway.

PROJECT TITLE: **Project title and RAC No."Repairing of Vesicovaginal Fistulae Using the Transabdominal Approach with Flap**

RAC # 2111 106

INVESTIGATORS: *Dr. Waleed Al Taweel (PI), Dr. Emad Rajih*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: To study the effect of trans-abdominal approach with flap in vesicovaginal fistula repair.

PROJECT TITLE: **Project title and RAC No."The Correlates of Sexual Dysfunction in Liver Transplantation Patients and the Impact of Management**

RAC # 209 1016

INVESTIGATORS: *Dr. Said Kattan (PI), Dr. Raouf Seyam (co-PI), Prof. Waleed Al Khudair, MD (co-PI), Dr. Ahmad El-Sakka, Dr. Mohamed Ibrahim Alsebayel, Dr. Alaa Moukhtar Hammad*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: The two components of studies will be cross sectional study of sexual dysfunction and quality of life in post transplant male patients and a prospective study to evaluate the impact of liver transplantation on sexual dysfunction and quality of life.

The Research Ethics Committee (REC) accepted the reply from the department of Urology to rectify the problem such as:

1. To immediately contact the previous patients and have them sign the consent form at a time convenient to them
2. Review the patient chart and document in the progress notes the consent and plan if not already stated
3. Insert the consent in the patient file
4. Amend the project to include Dr. Waleed Al Khudair as the principal co-investigator.

The Research Ethics Committee (REC) recommended the approval of the study for 6 months. The department submitted a request for publication/presentation of an abstract in an international meeting.

PROJECT TITLE: **The Effect of Alpha Adrenergic Blockers on the Ureter: an In Vivo Study in the Dog**

RAC # 2050 032

INVESTIGATORS: *Dr. Waleed Al Taweel, MD (PI), Dr. Raouf Seyam, Dr. Alaa Moukhtar, Hassan Aboul-Enein, Raafat El-Sayed, Falah Al-Mohanna*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: The project is conducted to study the effect of the drugs in the ureter. Alpha blocker adjuvant treatment to the ureteric stones is worthwhile as it facilitates the spontaneous passage leading to decreasing complications, less intervention and less analgesic use.

The Basic Research Committee (BRC) recommended for a revision of the proposal on the following concerns:

1. It is not clear to the Committee how the study proposal will be changed to accommodate smaller total number of animals used.
2. The study design is not clear and requires more detail
3. The study has many statistical limitations closely linked to overall design. The Committee recommended the inclusion of a statistician to help in the design of the study with sample size calculations and data analysis.
4. There is no control of each dose mentioned.
5. The proposal that is irrelevant to the study should be deleted

A memo containing a point to point reply to the concerns raised by the Basic Research Committee (BRC) will be presented to the reviewing committee.

PROJECT TITLE: **Microvascular Techniques in Surgery for Infertility and Erectile Dysfunction: Training of the Urology Staff**

RAC # 2082 001

INVESTIGATORS: *Dr. Raouf Seyam and Dr. Said Kattan*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: A training session amongst urologist in collaboration with the Comparative Medicine department to acquire the skills and techniques in the performance of microvascular surgery on rats particularly on its penis and testes.

The Animal Care and Used Committee (ACUC) has accepted the report as submitted and recommended the continued approval of the training program.

PROJECT TITLE: **Penile Autotransplantation in the Rat: Impact of Microsurgical Anastomosis of the Dorsal Neurovascular Bundle**

RAC # 2080 022

INVESTIGATORS: *Dr. Raouf Seyam (PI), Dr. Said Kattan, Dr. Lina Assad, Raafat El Sayed and Falah Hassan Almohanna*

PROJECT DESCRIPTION, PROGRESS, MAJOR FINDINGS: To evaluate the impact of microvascular anastomosis of the dorsal neurovascular bundle in the amputated penis on regaining erection and viability of the glans penis. The experiments will show the effect of different techniques of re-implantation on pharmacologically induced erection and on the histopathology of the cavernous tissues, urethra and skin.

The Basic Research Committee (BRC) and the Animal Care & Use Committee (ACUC) recommended the revised proposal with the related forms for approval.

Recently, a request for publication has been made based on the approved and on-going project.

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The Research Centre Logistics & Facility Management Office

The Research Centre Scientific Information Office

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