

2007





**THE**

**KING FAISAL SPECIALIST  
HOSPITAL AND RESEARCH  
CENTRE**

**RESEARCH REPORT 2007**



## ***Our Mission***

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*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 Director  
of KFSH&RC***

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*At the King Faisal Specialist Hospital and Research Centre, research is one of the core values of our institution. Our activities and agenda are dictated by the needs of the general population and steered by our ultimate goal of improving the quality of general health care and medical subspecialty services in the Kingdom.*

*As the public becomes progressively more informed about its healthcare needs and safety, expectations have shifted, increasing the demands on advanced and specialized care. To meet these growing needs, the Research Centre at KFSH&RC continues to expand and develop its facilities, programs and technology and remains today as one of the top research institutions in the region.*

*This Annual Report manifests our continued commitment to excellence in research. Many achievements have been made throughout the past year and this report highlights those initiatives undertaken in 2007. It maps our evolution as we continue to learn from and build on the successes of the programs we have conducted over the years. A major share of our success is attributed to the strong collaborative ties we maintain with highly regarded medical institutions worldwide, ensuring the exchange and cultivation of fresh new ideas.*

*Finally, our contributions are greatly amplified by the generous support from governmental and non-governmental entities – valuable support that continues to boost our confidence and drives us to excel.*



**Qasim Al-Qasabi, MD, FRCSI, FACS**

Chief Executive Director

King Faisal Specialist Hospital and Research Centre



***A message from the Executive Director of the  
Research Centre***

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*This annual publication is a tribute to the strength of our collaborations. The majority of the activities outlined here and the scientific publications resulting from these activities are outcomes of our active bridge-building initiatives. Of course, these are not possible without a focused research agenda and the unwavering support from our Government.*

*I am proud to witness our transformation into a premier research facility, but our work is not done. We must now work hard to raise our research programmes to a new level of success. We have to set our Vision towards the future and institute provisions that will allow us to adapt to change. We must meet with enthusiasm the challenges of developing new techniques to improve existing modalities and we must continue to advance research programmes that remain of paramount importance to the people of Saudi Arabia and its neighbouring countries.*

*Join us as we celebrate another year of productive research. Like most of you, I am encouraged at our progress. Until we ensure the sustainability of our goals and mission, until we succeed in our pursuit to improve the quality of healthcare in the Kingdom, work goes on.*



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



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# RESEARCH CENTRE



**BIOLOGICAL AND MEDICAL  
RESEARCH**



The Department of

# BIOLOGICAL AND MEDICAL RESEARCH

*D*uring the year 2007, the Biological and Medical Research is clearly on the verge of an exciting journey. Increasingly, all its sections are working together in transdisciplinary teams, combining expertise and experience in coordinated efforts to streamline scientific advancements, leading to a productive endeavour in the field of allergy and aerobiology, breast cancer, carcinogenesis, cell biology, coagulation, DNA repair and apoptosis, environmental health, laser medicine, biomedical chemistry, molecular virology and infectious diseases and proteomics.

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## *Acting Chairman*

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

## *Administrative Support Staff:*

Jorge Bautista (Technical Assistant,

Autoclave Operator)

Robyn Seamer (Hospital Assistant I)

Rita Sison (Hospital Assistant I)

Saif Zyada (Department Assistant)

Noemi Rosario (Hospital Assistant II) -

until May, 2007

Cheryl Mijares (Department Assistant,

Grant Employee - Allergy and Aerobiology)

Ma. Cecilla Perez (Hospital Assistant  
II, Grant Employee - Laser Medicine)

Gina Gonzales (Hospital Assistant II,

Grant Employee- Breast Cancer)

Hanan Shaarawi (Hospital Assistant II,

Grant Employee - MVID)

Major achievements for the year include:

- Development of indigenous allergen diagnostic kits for allergic patients.
- One of our papers which was published in *Tetrahedron* 2007 has been included in the list of the hottest articles of the year and rated "No. 1 in Top 25".
- Establishment of the Diabetes Research Program
- Demonstrated that the induction of the tumor suppressor p6INK4A gene in response to the carcinogenic UV light is under the control of the ATR protein kinase.
- Completed PSCDR funded project on the relationship between prenatal and postnatal lead exposure and early cognitive development.
- Succeeded in setting up a functional clinical proteomics laboratory.

The BMR Department continues to foster and support the education of future scientists. During the year, many graduates from national universities have received training in our laboratories. Our scientists continued to obtain external research funding globally.

We strive to be an internationally recognized department emphasizing an integrative approach to biological and chemical issues from molecular to global level. Our scientists are continuously expanding collaborations nationally and internationally, to further its image and broaden its influence.

In conclusion, the advances made in biology and medicine and the number of future projects have paved the way for a more productive year in 2008.

More information concerning each Section of the Department follows.

## Research Unit

# ALLERGY AND AEROBIOLOGY

*D*uring the year 2007, the Biological and Medical Research is clearly on the verge of an exciting journey. Increasingly, all its sections are working together in transdisciplinary teams, combining expertise and experience in coordinated efforts to streamline scientific advancements, leading to a productive endeavour in the field of allergy and aerobiology, breast cancer, carcinogenesis, cell biology, coagulation, DNA repair and apoptosis, environmental health, laser medicine, biomedical chemistry, molecular virology and infectious diseases and proteomics.

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**Head:****Syed M. Hasnain, PhD, FACAAl, FAAAAI****Members:**

Halima Al-Sini  
Abdulrahman Al-Sobhi  
Mubarak Al-Enizi  
Alanoud Al-Qassim  
Cheryl Mijares

## ACHIEVEMENTS

### 1. Project Completed

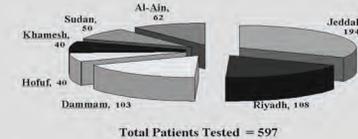
Successful completion of RAC approved project (RAC # 2060 006) Clinical and Efficacy Trial of Indigenous Allergens for Diagnostic Purposes.

In order to diagnose allergic patients with more relevant allergenic species, which they are directly exposed to, indigenous species were collected and prepared commercially along with other allergens under a collaborative project with M/s Immunotek, Madrid, Spain. Their allergens were tested in allergic patients in the region to evaluate the efficacy and reactivity. (Some graphs from the results are presented in Figures 1-4.

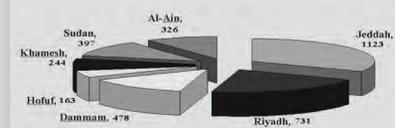
- The purpose of this clinical trial was to evaluate the efficacy of indigenous allergens diagnostic kits on patients having symptoms of inhalant allergies particularly asthma and allergic rhinitis.
- A panel of 30 different allergens mostly having indigenous origins and selected on the basis of aerobiological studies, conducted over the past 15 years at 10 locations of the country, was tested in allergic subjects by Skin Prick Test (SPT).
- Each participating physician and allergist conducted routine Skin Prick Test using our diagnostic materials in his clinic or hospital.
- Almost 600 allergic patients of all ages participated in this Clinical Trial of Indigenous Allergy Diagnostic Kits kingdom wide as well in the UAE and Sudan.
- No side effects or adverse reactions were reported by any allergists/physicians with any of the kits at any trial centre during the trial period.
- A few patients reacted to both positive and negative controls in Jeddah area only (probably human errors).
- Patients' consents were obtained as per Research Advisory Council approval.
- Indigenous Allergens were found to be highly effective in the *in vivo* diagnosis of many allergic patients in the Kingdom and abroad.
- Asthmatic and allergic individuals were found to be comparatively more sensitive to indoor allergens and indigenous spores than the outdoor allergens.
- While the cultural habits and climate appear to have played a role, socio economic conditions did not influence the overall sensitization pattern.



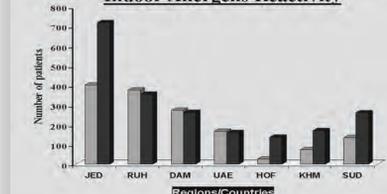
**Fig.2**  
**Number of patients Tested with Indigenous Diagnostic Kits**



**Fig.3**  
**Total Positive Reactions (Mild, Moderate and Severe) in Different Regions (n=597)**



**Fig. 4**  
**Regional Comparison of Outdoor and Indoor Allergens Reactivity**



The detailed result of this project was presented at the World Allergy Congress 2007 held in Bangkok, Thailand from 02-06 December 2007. The full publication is under preparation for submission to an international journal. The execution of this project was made possible by national and regional collaboration.

The following physicians and centres from the Kingdom of Saudi Arabia, United Arab Emirates and Sudan,

participated in the clinical trial as per approved guidelines of the Research Advisory Council. Patients' consent was obtained before any trial was conducted.

1. Mohammed Osman Gad-El-Rab, MD, FACAAl  
College of Medicine, King Saud University, Riyadh
2. Emad Koshak, MD, FACAAl, FAAAAI  
King Abdulaziz University Hospital, Jeddah
3. Hussein Al-Mehdar, PhD

- King Fahad Medical Research Centre, King Abdulaziz University, Jeddah
4. Tarek Geith, PhD  
Elaj Medical Services, Riyadh
  5. Emadia Alaqi, MD  
Children's Hospital, Riyadh Medical Complex, Riyadh
  6. Jamal Al-Gethmi, MD  
King Abdulaziz Hospital & Oncology Center, Jeddah
  7. Mohammed Al-Yamani, MD  
Maternity & Children's Hospital, Dammam
  8. Kamel Al-Abbad, MD  
Maternity & Children's Hospital, Dammam
  9. Rabea Khouqeer, MD  
Saad Specialist Hospital, Dammam
  10. Omer Abdulaziz, PhD  
Ribat University Hospital and Khartoom Sudan
  11. Shirina Alsowaidi, MD  
Faculty of Medicine & Health Sciences, UAE University, UAE
  12. Hussain Al Matar, PhD  
Al Imam Abdulrahman Bin Faisal Hospital, Dammam

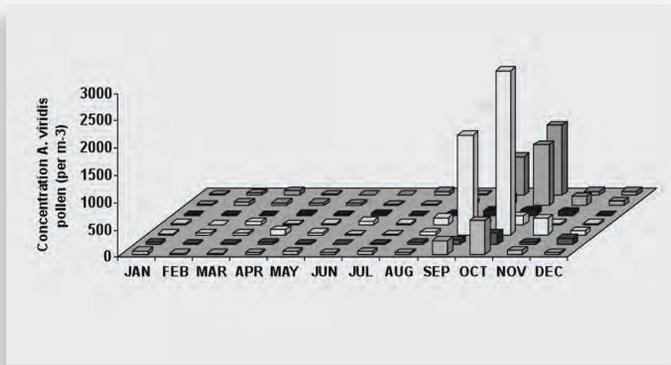


FIGURE 5



FIGURE 6

## 2. Project Approved

A research project entitled: Isolation, Purification and Immunochemical Characterization of Allergenic Proteins from *Amaranthus viridis* Pollen Grains, previously

approved by the, RAC #2050 029 was finally approved by KACST for financial support under grant ARP 27-11.

Description of this project has already been presented in the previous annual report; however, here is a short summary.

Pollen grains originating from roadsides and parkland weeds represent a major source of respiratory allergy worldwide. One of these weeds is *Amaranthus viridis*, a prevalent weed in Saudi Arabia. Therefore, it is anticipated that *A. viridis* may be a major cause of allergic diseases in sensitive patients as indicated by Saudi Aerobiological data which were collected from various Saudi Arabian cities under KACST projects AR-14-30 and AR 17-65.

In this project we intend to conduct a series of bio- and immunological experiments to characterize *A. viridis* allergens and their epitope determinants. Attempts will be made to purify western blot-specified allergens by conventional as well as advanced proteins purification methodologies. As it is well established that pollen

proteins allergenicity is partly encoded by their glycan chains, glycoprotein-staining tests periodic Schiff stain (PAS staining) for *A. viridis* SDS-PAGE separated proteins will indicate glycoproteins in the crude extract. ELISA and periodic acid oxidation of allergens will provide information on allergens epitope determinant, while ELISA-inhibition tests using known glycan structures will help to throw light on nature of epitope determinant(s). It is expected that the findings of this project will be beneficial for many allergy sufferers by inclusion of *A. viridis* in the diagnostic profile of the country for *in vitro* and *in vivo* diagnostic tests. These data will also be useful in future studies on indigenous weeds allergens in general and *A. viridis* in particular.

This project is being conducted in collaboration with Research Unit Proteomics of the Research Centre and Dr. Abdul Karim Alaya and Dr. May Al-Mohanna are co-investigators.

Figure 5 shows the maximum concentration of airborne *Amaranthus viridis* pollen in seven different regions of Saudi Arabia with concentration reaching to 3000/m<sup>3</sup> in October.



**FIGURE 6.** Courtesy of WAO on House Dust Mite workshop, Bangkok 2-6 December 2007.

### 3. Mobile laboratory for community services

In order to initiate a community oriented services program for the investigation of allergies and asthma causing agents in the ambient environment of patients or as a precautionary measures by at-risk patient (having family history of allergies and asthma or known to have previous allergic symptoms) protocols and logistics were finalized. For this purpose, a van was transformed into a mobile laboratory for visiting and collection of samples upon the request of physicians and individuals. A state of the art allergen-monitoring sampler was also installed on the van to collect outdoor allergens from various regions within short time. This installation of allergen sampler is the first of its kind in the Middle east, and perhaps, in the world.

### 4. Services Program Brochure

A revised new brochure for this purpose was also compiled for distribution to hospitals and clinics. The brochure can be viewed at the website: <http://bportal.kfshrc.edu.sa/wps/portal/RC> (Click Biological and Medical Research then Allergy and Aerobiology).

### 5. Reviews

The Unit head acted as reviewers of various national and international journals.

### 6. Training and Education

The following undergraduate and postgraduate Saudi candidate were trained in the laboratory.

- Alanoud Al-Qassim
- Fatmah Ali Al-Masrahi
- Al-Obaied, Hussah
- Al-Yami, Nouf
- Al-Beshi, Najja

Mr. Abdulrahman Al-Sobhi, Research Technician, Allergy and Aerobiology Research Unit, attended a House Dust Mite Workshop organized by the WAO-World Allergy Organization in Bangkok, Thailand. A model of House Dust Mite movement in the bed is presented in Fig. 7. The house dust mites are a major source of allergic diseases indoors in humid areas all over the world. In Saudi Arabia certain parts in western, northwestern and southern part have high content of dust mites.

### FUTURE RESEARCH DIRECTION

The Section will continue its endeavors to search and disseminate indigenous causes, immunotherapeutic treatment and/or prevention of increasing prevalence of allergy and bronchial asthma in the kingdom and to serve the community by bench to bedside services and products.

We hope to initiate services program as proposed above and begin collection and processing of pollen and spores for production of kits.

### PUBLICATIONS

- Hasnain, SM., Khatija, F., Al-Frayh, AR.: "Prevalence Of Airborne Allergenic *Amaranthus Viridis* Pollen In Seven Different Regions Of Saudi Arabia". *Annals of Saudi Medicine*; 27(4): 259-263.
- Hasnain, SM., Katelaris C., Newbegin Ed, Singh AB.: "Aeroallergen Monitoring Standard for the Asia Pacific Region". *World Allergy Organization 2007* pp. 1-26
- Hasnain, SM. Khatija, F., Al-Frayh, AR, Koshak, E. "An Outdoor Aeroallergen Calendar of Saudi Arabia, Dammam, Qassim, Jeddah and Riyadh". *Saudi Medical Journal*. Manuscript No. 20070211. (Accepted with revision).

### In Preparation

- Hasnain, SM. and Al-Frayh, AR..RAC approved #2060 006 - Indigenous Allergens in Saudi Arabia: Efficacy of Diagnostic Kits.

### Invited Lecture

- Hasnain, SM. Aeroallergens – How to Express your Data. WAO-World Allergy Congress 2007. Bangkok, Thailand. 2-6 December 2007.

### Presentation and Conferences

- Hasnain, SM., and Al-Frayh, AR. IgE Mediated Human Sensitization to Indoor Particles in Saudi Arabia. International Congress of Toxicology, Montreal, Canada, 15-19 July 2007.
- Hasnain, SM, Al-Frayh, AR., Gad-El-Rab, MO. Prevalence and Sensitization to Weeds Pollen in Saudi

- Arabia. World Allergy Organization – World Allergy Congress 2007 Bangkok, Thailand. 2-6 December 2007.
- Hasnain, SM. Al-Frayh, AR. Subiza, JL. Al-Sedairy, ST. Indigenous Allergens in Saudi Arabia: Efficacy of Diagnostic Kits. WAO – World Allergy Congress 2007, Bangkok, Thailand. 2-6 December 2007.
  - Al-Frayh, AR and Hasnain, SM. Prevalence of Bronchial Asthma in Children in Saudi Arabia. WAO – World Allergy Congress 2007, Bangkok, Thailand. 2-6 December 2007.
  - Hasnain, SM., Noori, Y., Waqar A. Prevalence of Allergies and Asthma in Pakistan. WAO – World Allergy Congress 2007, Bangkok, Thailand. 2-6 December 2007.

## Research Unit

# BIOMEDICINAL CHEMISTRY

The main target of this unit is dealing with applied Enzymology or Biocatalysis in chiral drug developments. In the meantime, we are providing research advices and chromatographic analysis for different research groups at the Research Centre and the Hospital (Department of Urology). The analysis is ranging from pharmaceutical compounds to plant extract used in the treatment of breast cancer.

We are also preparing different chiral building blocks used in numerous pharmaceutical compounds by using two approaches. The first consists of using lipase enzymes as natural catalysts to access to the desired enantiomerically pure compounds by kinetic resolution of the corresponding racemates. This approach is used in the access of racemic anti-inflammatory acidic drugs and cardioselective beta blockers in their single enantiomeric pure form. The second approach consists of the design of chiral rhodium (III) catalysts able to catalyze the asymmetric access to enantiomerically pure/enriched cyclopropane derivatives as chiral entities for an effective drug, which will be used, for the inhibition of breast cancer cells (KACST Project Nr (AT-08/25), RAC Nr 2010 044).

We are also working with physicians on studying the effect of alpha-blockers on the canine ureter (Cooperation with the department of Urology, RAC project No 2050032).

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**Head:****Mohammed Al-Ahdal, PhD****Members:**

Ashraf Ghanem, PhD

Ebtessam Al-Humaidan, BSc

## RESEARCH PROJECTS/ ACTIVITIES

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**1. KACST Project Nr (AT-08/25), RAC Nr 2010 044 entitled: From Enzymes To Chiral Metal Catalysts: Asymmetric Access To Enantiomerically Pure/Enriched Pharmaceuticals And Related Biologically Active Compounds.**

Budget: 476.600.00 SR

**Status:** Ongoing

This project is dealing with the chiral drug discovery using lipases and chiral rhodium catalysts in combinatorial approach. The new chiral building blocks accessed by lipases and rhodium catalysts will be used in the discovery of a new efficient drug able to inhibit breast cancer cells.

**2. RAC project No: 2050032, entitled "Studying The Effect Of Alpha-Blockers On The Canine Ureter".**

In cooperation with the Department of Urology

**Status:** Ongoing.

**3. KACST project No: 02-1428**

We recently got an approval from KACST to finance a project dealing with enzymology and biocatalysis. This project consist of the first production of Saudi lipase enzyme and its application in pharmaceutical industry.

Approved budget: SR 2,500,000 (two and half million Saudi Riyals)

## FUTURE RESEARCH DIRECTION

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1. Production of Highly Thermostable Lipase enzymes from Thermophilic Bacterium Isolated from Saudi Soil for industrial clinical and pharmaceutical applications.
2. The development of tailor-made biocatalysts

suitable for industrial production of pharmaceutical compounds.

3. Extensive use of Chirality in drug discovery and clinical applications.
4. Provide Chromatographic services for medical department.

## ACTIVITIES

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1. Our unit did participate in Ibn Sinai Program For Science and we did host two students for one month at our lab.
2. We hosted Ms Hessah Al-Shammari from King Khaled foundation to be trained for her future MSC program in UK.

## PUBLICATIONS

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- Ashraf Ghanem "Trends In Lipase-Catalyzed Asymmetric Access To Enantiomerically Pure/Enriched Compounds" *Tetrahedron* 2007, 63, Pages 1721-1754.
- Ashraf Ghanem "Exploring Solvent Versatility In Bonded Cellulose-Based Chiral Stationary Phase For The Enantioselective Liquid Chromatographic Resolution Of Racemates" *Journal of Separation Science* 2007, 30(7), 1019-1028.
- Ashraf Ghanem "Application of C-11 Chirasil-dex in Enantioselective Separation of Barbiturates" *Analytical Chemistry Insights* 2007, 2, 75-80.
- Ashraf Ghanem, Ebtessam Al-Humaidi "Chiral Recognition Ability And Solvent Versatility Of Bonded Amylose Tris-(3,5-Dimethylphenylcarbamate) Chiral Stationary Phase: Enantioselective Liquid Chromatographic Resolution Of Racemic N-alkylated Barbiturates And Thalidomide Analogs. *Chirality* 2007, 19(6), 477-484.
- Ashraf Ghanem, Farrag El-Beahiry, Mohammed Al-Ahdal "Direct Enantioselective HPLC monitoring of Lipase-Catalyzed Kinetic Resolution of Racemates in Non-standard Organic Solvents" *Chromatographia* 2007, Volume 65, Numbers 11-12, pages 681-686.



Structure of *Mucor miehei* lipase in the open form showing  $\alpha/\beta$ -hydrolase fold" motive known from serine proteases. When the "lid" is open, the catalytic triad at the active center (red) is becomes accessible for substrate (normally triglycerides).



A figure showing the simple definition of "Chirality" the object and its mirror image (right and left hand). Both are mirror image of each other but they are not superimposable



## Research Unit

# BREAST CANCER RESEARCH

*B*reast Cancer has a major impact on the health of women worldwide including Saudi Arabia, where it is considered the most frequently diagnosed cancer and the leading cause of cancer deaths. It is hence imperative to conduct thorough research on this disease to elucidate its genetic and environmental causes, which are important for cancer prevention and treatment. We anticipate to conduct a multidisciplinary research program aiming at understanding the causes of breast cancer in relatively young population and to investigate novel therapeutic approaches. The aim of our unit is to establish molecular profiling of breast tumors in Saudi population to uncover the heterogeneity of this disease and to offer novel insight into tumorigenesis and therapy management.

.....

**Head:****Suad Bint Mohamed Bin Amer, PhD****Members:**

Maimoona Nirmal  
Hatim Jeprel  
Gina T. Gonzales  
Asma Nofal

## RESEARCH PROJECTS

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### 1. Identification Of Environmental And Genetic Factors That Influence Breast Cancer Development And Therapy In Saudi Females (RAC # 2031091)

In collaboration with KACST

**Investigators:** Suad Bint Mohamed Bin Amer, Taher Al –Tuweigeri, Asma Tulbah, Dahish Ajarim and Osama Malik

#### Project description

We aim to establish the consensus gene profile for Saudi population by using Micro Array technique and 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 aim to study the potential of 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

##### *Sample collection*

Collection of freshly resected Breast tumors and tumor adjacent tissues, lymph node, blood, and FNA samples is being done in collaboration with clinicians and pathologists by using the internationally standardized protocol.

##### *Gene expression studies*

We have successfully established the gene profiling of 90 samples so far. We used unsupervised hierarchical clustering analysis in order to cluster patient samples according to the genes that are differentially expressed. Several other statistical tools were also applied on the Affymetrix data to generate significant results.

Our data are already indicating promising results, whereby it is possible to classify the patients according to different clinicopathological criteria such as Her2/ Neu status, ER status and aggressiveness of disease. Clustering of genes according to ER and PR status show some common genes which indicate that there are common pathways between the two groups. Co-relationship between different parameters ER, PR and LIVI (lymphatic and vascular invasion) also indicates the involvement of different pathways. Genes common between the groups Her2 pos. VS Her2 neg. & Her3 pos. VS Her3 neg. indicate more heterogeneous nature of Her2/neu receptor.

##### *Establishment of Sample Management System*

A sample management data base was established in collaboration with BESC department. This database will prove to be an extremely valuable resource for clinicopathological information, sample storage information and patient medical history.

### 2. Determination Of The Role Of Several Radio-Flourinated Bombesin Peptides As A Molecular Imaging Agent For The Detection Of Breast Cancer (RAC # 2030058)

In collaboration with Cyclotron department

**Investigators:** Ibrahim Al Jamaz, Suad Bint Mohamed Bin Amer

#### Project description

Breast cancer cell lines are being established and maintained in order to determine the role of several radio-flourinated Bombesin peptides as a molecular imaging agent for the detection of Breast Cancer.

## **FUTURE RESEARCH DIRECTION**

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We aim to establish gene expression profiles of at least 120 samples tissue in order to generate significant results which can be compared to international data. We also intend to generate the gene profiles by using FNA samples. Another future direction includes study of Proteomic profiles of breast cancer samples.

## **PUBLICATION**

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- Zakia Maqbool PhD, Amal Gattan MSc, Maimoona Nirmal BPharm, Syed S. Hussain PhD, Hatim Jeprel BSc, Asma Tulbah MD, Osama Malik MD, Taher Al -Tuweigeri MD, Suad M. Bin Amer PhD, Gene expression profiling in women with breast cancer in a Saudi population.



## Research Unit

# CARCINOGENESIS

The identification and characterization of various environmental and dietary factors in cancer development continues to be an important and strategic goal of our Research Unit in order to develop effective measures for the prevention and control of cancers. Our major priorities are to understand the etiology of various human cancers in the Kingdom and subsequently design and implement the strategies for their prevention and therapies.

Biomarkers play an important role in understanding the various aspects of biochemical mechanism(s) of complex cellular pathways. In our continuous effort to explore the novel cancer chemopreventive agents, we observed differential response with a variety of natural plant-derived chemicals, marine compounds and synthetic antiviral aminopyrazoloquinoline derivatives in human normal and breast cancer epithelial cell lines using DNA adducts and cell cycle progression markers as biomarker of chemoprevention. An inverse correlation between the degree of apoptosis and modulation of benzo[a]pyrene-derived DNA adducts by these compounds was noticed which seems to hold true in the cancer cell lines only. Furthermore, differential modulation of various tumor suppressor and apoptosis-related genes by these compounds in both normal and cancer cell lines was observed. An attempt to establish a correlation between these biomarkers is underway.

.....

**Head:****Fahad M. Al-Khodairy, PhD****Members:**

Ahmad A. Al-Dakan, BSc

Muhammad Kunhi, MSc

## RESEARCH PROJECTS

**Project title: Etiology And Prevention Of HRT (Hormone Replacement Therapy) -Induced Gynecological Cancers: An *In vitro* Study. RAC # 2040 033 (KACST Ms 10-5)**

**Investigators:** Fahad M. Al-Khodairy, Jamal M. Arif and Muhammad Kunhi

### Project description

Despite the reduced risk of osteoporotic fractures, cardiovascular and Alzheimer's diseases by HRT, only 5% of postmenopausal women are currently taking HRT in Saudi Arabia because of a perceived fear of developing breast and endometrial cancers. However, lack of known mechanism(s) of action of equine estrogens (EE), major constituents of HRT formulations, to understand the etiology of estrogen-sensitive cancers has severely limited the efforts to design the prevention strategies for the HRT users with minimal deleterious side-effects.

This proposal using the established cell lines from breast, endometrium and ovary will study the DNA damaging potentials of the selected EE, namely equilin and equilenin and their metabolites, due to their preponderance in the HRT formulation (Premarin) in order to understand the relative mechanism(s) and etiology of breast, endometrial and ovarian cancers.

### Project progress

The following estradiol compounds namely:

1. 3-Hydroxy-1,3,5(10),7-Estratetraen-17-one ,
2. 1,3,5(10),6,8-Estrapentaen-3-OL-17-one sulphate, sodium salt,
3. 1,3,5(10)Estratrien-2,3,17 b-Triol,
4. 1,3,5(10)Estratrein-2,3-Diol-17-one and
5. 1,3,5(10) Estratrien-3,17b-Diol

were tested on ATCC cancer cell lines like , mcf-7, mda-mb-231, Ovacar and Uterine cancer with different doses and different time points and apoptosis and cell cycle analysis were done as end points by using flow cytometry.

**2. Project title: Role Of Novel Compounds From Plant, Marine And Microbial Sources In The Breast Cancer Prevention. RAC# 2030041**

**Investigators:** Fahad M. Al-Khodairy, Jamal M. Arif, Osama Ahmad Al-Malik, Mohammad Kunhi

### Project description

To screen a variety of novel compounds isolated from diverse natural sources using the DNA adducts and apoptosis as biomarkers for their efficacy against breast cancer development.

### Progress

Several of the natural and synthetic compounds were analyzed for their potential of modulating the BP-DNA adducts using MCF-7 cells and cell cycle progression markers. Erysolin (50 uM), looks quite promising chemopreventive agent as it almost abolished the BP-DNA adduct formation and causing 50-70 % apoptosis in MCF-7 and MDA-MB-231 cell lines. However, a significant number (60-80%) of the normal breast epithelial cell lines (MCF-10A and MCF-12A) also undergone apoptosis which may undermine erysolin's potential as a chemopreventive agent. All 30+ compounds were tested using rat liver microsomes against the *in vitro* BP-DNA adduct modulation

The selected compounds were further tested for their anticancer potentials using cellular viability and apoptosis in various human breast cancer and normal epithelial cell lines obtained from ATCC (USA). The apoptosis has been used as a novel target for screening the new compounds for their anticancer potential. We found differential response depending on the type of cell lines and compounds. Solanine and rysolin showed potent apoptotic activities against both the normal and cancer cell lines. In fact, the apoptotic effect was more pronounced in the normal cells which may make them unsuitable for chemopreventive aspect.

In order to correlate the two well-known biomarkers (apoptosis and DNA adducts) for the screening of new compounds, we also assessed these compounds for their anticancer potential using DNA adducts as biomarker. In principal, those compounds, which can induce apoptosis should concomitantly show reduction in the BP-DNA adduct levels in order to be designated as probable anticancer. However, it showed differential response in terms of apoptosis in MCF-7 cells. Only solanine (50 M) was found to induce about 40% apoptosis. In contrast the BP-DNA adduct was modulated by 25% in the MCF-7 cells by solanine (50 M). Likewise thymoquinone showed no apoptosis in either of the cell lines. while it induced the BP-DNA adduct data by 350% . Nevertheless, this seems to hold true for erysolin in case of cancer cell lines however, it was inconclusive in the normal cells

because of the insufficient recovery of DNA from the cells which were killed

In conclusion, it suggests that these two biomarkers are not in good agreement with each other to provide conclusive evidence for any compound to be anticancer. We believe that it would be the first report on the correlation of these two biomarkers in the screening of the new compounds and would bring thoughtful debate on the use of these two biomarkers.

## FUTURE RESEARCH DIRECTION

Our KACST funded project on the effect of equine estrogens on the gynecological cancers using human breast, endometrial and ovarian cancer cell lines *in vitro* and our cumulative efforts from these and other RAC approved projects hopefully will provide a lead in the search of new compounds with strong anticancer potential against certain cancers prevalent in the Kingdom.

## PUBLICATIONS

### A. Full length

- Arif JM, Kunhi M, Subramanian M, Bekit A, El-Sayed O, Hussei K, Aboul-Enien H, and Khodairy F. Cytotoxic And Genotoxic Potentials Of Newly Synthesized Antiviral Aminopyrazo-Loquinoline Derivatives. *Medicinal Chemistry Research*, (Accepted for publication in 2007).
- Arif JM, Kunhi M, Bekhit AA, Subramanian MP, Al-Hussein K, Aboul-Enein HY, Al-Khodairy FM. Evaluation Of Apoptosis-Induction By Newly Synthesized Phthalazine Derivatives In Breast Cancer Cell Lines. [Journal Article] *Asian Pacific Journal of Cancer Prevention*: Apjcp. 7(2):249-52, 2006 Apr-Jun
- Arif, J.M., Dresler, C., Clapper, M.L., Gairola, G.C., Srinivasan, C., Lubet, R.A., and Gupta, R.C. Lung DNA Adducts Detected In Human Smokers Are Unrelated To Typical Polyaromatic Carcinogens. *Chem. Res. Toxicol.* 19:295-299, (2006).

### B. Abstracts

- Arif, J.M., Kunhi, M., Siddiqui, Y.M., El-Sayed K.A., Orabi, K.Y., Al-Ahdal, M.N. & Al-Khodairy, F.M. Microsomal Activation of Marine Compounds Leading To Modulation Of The Carcinogen-DNA Adduct Formation: Role Of Cytochrome P450s. In: 13<sup>th</sup> AEK/AID Cancer Congress, Wurzburg, March 13-16, 2005.
- Arif, J.M., Kunhi, M., Manogaran, P.S., Siddiqui, Y.M., Al-Ahdal, M.N., Al-Hussein, K. & Al-Khodairy, F.M. Effect of Safed Musli (*Chlorophytum borivilianum*) on the cell kinetics and apoptosis in the human breast cancer cell lines. In: Int. Conference on Promotion and Development of Botanicals with International Coordination: Exploring quality, safety, efficacy and regulation, Kolkata, India, Feb. 25-26, 2005.
- Siddiqui, Y.M., Arif, J.M., Kunhi, M., Al-Ahdal, M.N., & Al-Khodairy, F.M. Potent Antiviral Effect of Safed Musli (*Chlorophytum borivilianum*) on Poliovirus Replication. In: Int. Conference on Promotion and Development of Botanicals with International Coordination: Exploring quality, safety, efficacy and regulation, Kolkata, India, Feb. 25-26, 2005.
- Arif, J.M., Kunhi, M., Siddiqui, Y.M., Al-Ahdal, M.N., & Al-Khodairy, F.M. DNA Adducts As Biomarkers of Cancer Induction And Prevention. In: Int. Symposium on Diet in Causation & Prevention of Cancer and XXX Annual Conference of Environmental Mutagen Society of India, Lucknow, India, March 17-19, 2005.
- Arif, J.M., Kunhi M. and Al-Khodairy, F.M. Apoptosis, DNA Damage and Toxicogenomics: Role in Screening of New Compounds. In: Int. Conference on Toxicology Environmental and Occupational Health, Lucknow, India. Nov. 14-17, 2005.



## Research Unit

# CELL BIOLOGY AND CONFOCAL MICROSCOPY

Latest figures reveal a 24% prevalence of Type 2 Diabetes in the Saudi population. 60% of Saudi Cardiovascular patients suffer from Diabetes. Diabetes is a progressive disease preceded by hypertriglyceridemia, hyperglycemia, hypertension, impaired Glucose tolerance and central adiposity. These disorders constitute the Metabolic Syndrome, which is present in 42% of the adult male 37% of the adult female Saudi population. Our Diabetes Program consists of seven main projects: [1] Diet-induced Metabolic Syndrome and Type 2 Diabetes in a rodent model. [2] *in vitro* metabolic studies into the etiology of Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Hepatic Steatosis (NASH) in hepatocytes. [3] Type 2 Diabetes and cognitive dysfunction in a feline model. [4] Food Frequency Questionnaire (FFQ) and relation to Body Mass Index (BMI), Waist-to-Hip Ratio (WHR) and Total Body Fat in Saudi School Children. [5] Trial of LAF293, a new anti-Diabetes drug in Saudi Diabetic patients. [6] Whole Genome Scanning for Diabetes associated genes. [7] Lentiviral Gene delivery of the anti-inflammatory agent Vaccinia Virus Complement Protein (VCP) in a small-animal model. Our Cardiovascular Research Program continues with [i] further characterization of our Ovine Model of Reversible Cardiac Failure, and [ii] Serial Analysis of Gene Expression (SAGE) of genes involved in Xenorecognition of foreign antigens.

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### **Head:**

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

### **Members:**

Kate S Collison, PhD  
 Mohammed Al-Johi PhD  
 Zakia Maqbool, PhD  
 Soad Saleh  
 Razan Bakheet  
 Angela Inglis  
 Nadine Makhool  
 Rhea Mondreal  
 Rana Al-Rabiah  
 May Al-Obaidallah  
 Marya Zia  
 Reem Al-Hejailan

## RESEARCH PROJECTS/ACTIVITIES

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**Project title: RAC#2060 007 Metabolic Syndrome, Diabetes And Cognitive Decline: Effect Of Dietary Components On Insulin Resistance, Hyperlipidemia, Inflammation And Cognition In A Rodent Model.**

**Investigators:** Collison, K; Saleh, S; Inglis, A; Bakheet, R; Al-Johi, M; Maqbool, Z; Makhool, N; AL-Abaidallah, M; Al-Rabiah, R; Mondreal, R & Al-Mohanna, F.

### Project description

Metabolic syndrome, diabetes and cognitive decline: effect of dietary components on insulin resistance, hyperlipidemia, inflammation and cognition in a rodent model.

### Progress

This study is 80% completed, with evidence of significant correlations between dietary type and cognitive performance already apparent. Study is on-going.

**2. Project title: RAC# 2061027 Survey Of Dietary Habits In The Saudi Population: Correlation Of Diet With Body Mass Index And Waist-To-Hip Ratio As Indices For Risk Factors For The Development Of The Metabolic Syndrome.**

**Investigators:** Collison, K; Subhani SN; Zia, M; Shoukri, M & Al-Mohanna, F.

### Project description

Food Frequency Survey of dietary habits in the Saudi population: correlation of diet with Body Mass Index (BMI) ,Waist-to-Hip Ratio (W-T-H) and total body fat as indices for risk factors for the development of the Metabolic Syndrome.

### Progress

6270 individuals have been surveyed and entered into the database. Using these, we have noted several statistically significant dietary factors which adversely correlate with increased BMI and W-T-H ratio. Study is on-going.

**3. Project title: *In Vitro* Metabolic Studies Into The Etiology Of Nonalcoholic Fatty Liver Disease (NAFLD) And Nonalcoholic Hepatic Steatosis (NASH) in**

### Hepatocytes.

**Investigators:** Collison, K; Saleh, S; Bakheet, R; Inglis, A; Al-Rabiah, R; & Al-Mohanna, F.

### Project description

HepG2 liver cells develop insulin resistance, mitochondrial dysfunction, endoplasmic stress and increased triglyceride synthesis upon exposure to high fructose corn syrup in a dose- and time-dependent manner. The liver is the primary route of metabolism of fructose, and Nonalcoholic fatty liver disease is a new and increasingly prevalent metabolic disease (NAFLD) of the industrialized world. A causal link between HFCS and NAFLD has yet to be established.

### Progress

Manuscript submitted.

**4. Project title: RAC# 2060 037 Metabolic Syndrome, Diabetes, and Cognitive Decline in a Feline Model.**

**Investigators:** Collison, K & Al-Mohanna, F.

### Project description

Feline diabetes closely resembles human type 2 diabetes. We will induce insulin resistance and metabolic syndrome in test subjects using specific dietary manipulation of animals bred from female cats consuming the tested diets. Cognitive studies will be performed.

### Progress

**Phase 0:** Ensuring consumption of the 4 diets – Acceptability studies completed

**Phase 1:** Breeding – Females will be placed on appropriate diet and mated – approximately 2 months – ongoing.

**Phase 2:** Weaning – Kittens remain with female on appropriate diet until weaning (approximately 3 months of age)

**Phase 3:** Initial assessment – Measures of blood chemistry, body structure and fat density (DEXA's) and brain structure are taken. (after weaning)

**Phase 4:** Initial cognitive assessment – Kittens are tested in positional learning and reversal task – and are trained in object discrimination and reversal task

**Phase 5:** Six month assessment – again do DEXA's, MRI's and training on one cognitive test.

**5. Project title: Whole Genome Scanning for Diabetes; Associated Genes**

**Investigators:** Al-Mohanna, F.

**Project description**

Whole Genome Scanning for Diabetes; associated genes.

**Progress**

Ongoing.

**6. Project title: RAC# 2050 046 Vaccinia Virus Complement Control Protein (Vcp): Potential To Prevent Damage To Xenoreactive Cells**

**Investigators:** Collison, K; Al-Johi, M & Al-Mohanna, F.

**Project description**

VCP is a potent anti-inflammatory molecule. We will use the lentiviral Gene Delivery System to ascertain its anti-inflammatory effects in a small-animal model.

**Progress**

The Lentiviral constructs have been completed. Viral Titres are being made. Once purified, we will establish which of the 3 different gene delivery routes will be the most effective in a rodent model.

**7. Project title: LAF237 Drug trial in Type 2 Saudi Diabetic Patients**

**Investigators:** Collison, K; Al-Rubbean, K & Al-Mohanna, F.

**Project description**

Current pharma begins to fail the average diabetic patient between 10 and 20 years into the disease. Better and more effective drugs are urgently required in order to avoid some of the more devastating and costly consequences of poorly controlled type 2 diabetes, namely nephropathy, neuropathy and amputation of necrotic tissue. LAF237 (Vildagliptin, Novartis) is an oral DPP-IV inhibitor which has completed Phase III clinical trials and is due for FDA filing in 2006. In trials, LAF237 demonstrated a strong efficacy in lowering

HbA1c levels, improving pancreatic islet cell function and insulin sensitivity, whilst maintaining neutral effect on body weight.

**Progress**

Recruiting patients.

**8. Project Title: Serial Analysis Of Gene Expression (SAGE) Of Genes Involved In Xenorecognition Of Foreign Antigens**

**Investigators:** Collison, K, Saleh, S. Inglis A & Al-Mohanna, F.

**Project description**

The use of Serial Analysis of Gene Expression (SAGE) of genes involved in Xenorecognition of foreign antigens. Our previous studies indicate that differentiated leukocytic cell lines are capable of xenoantigen recognition, whereas undifferentiated cells are not. We have used SAGE to generate libraries of genes whose expression levels change in response to differentiation signals. It is to be expected that amongst these genes will be a percentage which are involved in the xenorecognition process and accompanying signal transduction pathway.

**Progress**

These genes are now in the process of being analysed.

**9. Project Title: RAC#2000 002 Oxford Heart Project: Reversible Model Of Ovine Heart Failure**

**Investigators:** Quittaineh, M; Collison, K; Al-Mohanna, FA

**Project description**

Use of aortic banding to induce gene expression of proteins involved in Myocyte remodelling.

**Progress**

Biopsy specimens were taken at all stages in addition to full work-up and ECG monitoring. Banding progressively loosened to reverse procedure and further biopsy material taken. RNA, DNA and protein samples stored for analysis.

## PUBLICATIONS

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- Moorjani N, Ahmad M, Catarino P, Brittin R, Trabzuni D, Al-Mohanna F, Narula N, Narula J, Westaby S. Activation of apoptotic caspase cascade during the transition to pressure overload-induced heart failure. *J Am Coll Cardiol.* 2006 Oct 3;48(7):1451-8. Epub 2006 Sep 12.
- Moorjani N, Catarino P, Trabzuni D, Saleh S, Moorji A, Dzimiri N, Al-Mohanna. Upregulation of Bcl-2 proteins during the transition to pressure overload-induced heart failure. *Int J Cardiol.* 2007 Mar 2;116(1):27-33
- Thestrup-Pedersen K, Parhar R, Wu K, Bertilsson PA, Meyer B, Abu-Amero S, Hainau B, Aleisa A, Alfadley A, Hamadah I, Alajlan A, Al-Hussein K, Al-Mohanna F. Skin-homing CD8+ T lymphocytes show preferential growth *in vitro* and suppress CD4+ T-cell proliferation in patients with early stages of cutaneous T-cell lymphoma. *Acta Derm Venereol.* 2007;87(2):118-26.
- Bouchama A, Kwaasi A, Dehbi M, Al Mohanna F, Eldali A, El-Sayed R, Tbakhi A, Alzahrani AS, Roberts AG. Glucocorticoids do not protect against the lethal effects of experimental heatstroke in baboons. *Shock.* 2007 May;27(5):578-83
- Abu-Amero KK, Al-Mohanna F, Al-Boudari OM, Mohamed GH, Dzimiri N. The interactive role of type 2 diabetes mellitus and E-selectin S128R mutation on susceptibility to coronary heart disease. *BMC Med Genet.* 2007 Jun 20;8:35.

## Research Unit

# DNA REPAIR AND APOPTOSIS

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. The major goal of this research section is to participate in understanding the fundamental processes that regulate the equilibrium between cell proliferation and cell death and to identify and characterize molecular biomarkers for cancer staging/grading. We are also interested in discovering novel and efficient drugs that can be used for prevention and/or treatment of cancer.

The major findings of this year are the following:

- We have shown that curcumin is a potent anti-medulloblastoma agent, and also an enhancer of the killing effect of cisplatin and ionizing radiation against these tumor cells.
- We have also demonstrated that the induction of the tumor suppressor p16<sup>INK4A</sup> gene in response to the carcinogenic UV light is under the control of the Atr protein kinase.
- The majority of breast cancer stromal fibroblasts express high levels of the cancer biomarker survivin and are highly resistant to the killing effect of UV light and the chemotherapeutic agent cisplatin.

### **Head:**

**Abdelilah Aboussekhra, PhD**

### **Members:**

Nisreen M. Al-Moghrabi, PhD  
Siti Faujiah Hendrayani, MSc (Grant  
employee)  
Ibtehaj S. Al-Sharif, BSc  
Nujoud Al-Yousef, BSc

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## RESEARCH PROJECTS

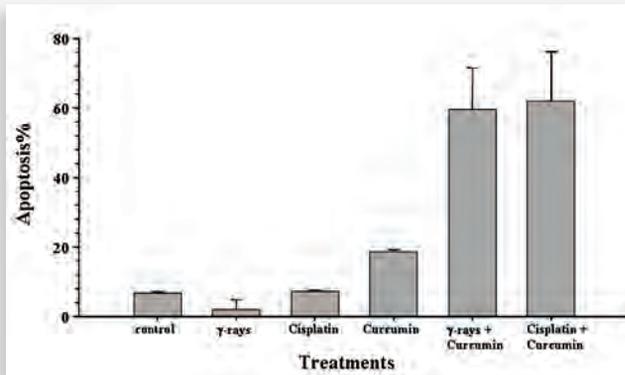
**Project title: Cellular And Molecular Characterization Of Medulloblastoma In Saudi Patients: Correlation With Prognosis And Therapy. RAC # 2050016**

**Investigators:** A. Aboussekhra (PI), Y. Ghafaga, A. Al-Kofidy, H. Al-Hinde, E. Al-Shail, M. Hassounah, N. El-

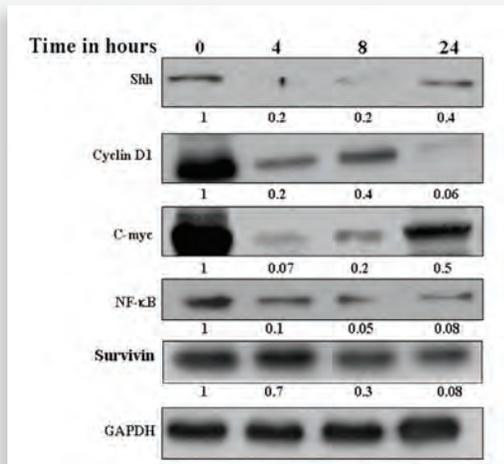
Kum, N. Al-Yussef and K. Habaybia

### Project description

Our main objective is to establish and characterize primary cell lines from medulloblastomas derived from Saudi children and try to identify molecular markers that could be correlated with prognosis and hence can be used as a disease-risk stratification tool. To achieve this goal, we decided to analyze the status and expression levels of different genes including the MYCC oncoprotein, the tumor suppressor TP53-ARF pathway, the receptor tyrosine kinase TRKC oncoprotein and the protein kinases Aurora A and B. Finally, we would attempt to correlate these with the cellular and tumor responses to the therapeutic agents, Vincristine, Lomustine and Cisplatin, used in the treatment of medulloblastoma, and with the treatment outcome.



**FIGURE 1.** Curcumin potentiates the effects of cisplatin and  $\gamma$ -rays by inducing apoptosis in medulloblastoma cells. The proportions of apoptotic cells were determined using the annexinV/PI-Flow cytometry technique.



**FIGURE 2.** Curcumin down-regulates the expression of different oncoproteins implicated in the carcinogenesis of medulloblastoma. Cells were treated with 40  $\mu$ M of curcumin for the indicated periods of time.

### Progress

20 primary medulloblastoma cells were developed and characterized. In response to curcumin, most of these cells showed high sensitivity and apoptotic response. Interestingly, curcumin potentiated the killing effect of both cisplatin and  $\gamma$ -rays (Figure 1), indicating that it can be used as a synergistic therapy. The effect of curcumin on medulloblastoma cells was through the inhibition of two major tumorigenesis pathways NF- $\kappa$ B and Sonic Hedgehog as well as the down regulation of the antiapoptosis protein survivin (Figure 2).

**Project title: Study Of The Role Of Tumor Suppressor Genes In Dna Repair And Cell Cycle Checkpoints. RAC # 990 025**

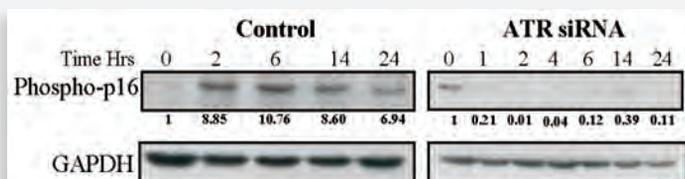
**Investigators:** A. Aboussekhra (PI), N. Al-Moghrabi, M. Al-Mohanna, K. Al-Hussein and F. Al-Khodairy

**3. Project title: Functional Identification Of Breast Cancer Genetic Predisposing Factors. KACST/RAC# 2031 091**

**Investigators:** A. Aboussekhra (PI), A. Tolbah, T. Twigery, O. Al-Malik, D. Ajareem, and S. Dermime

### Project description

To study the role of stromal fibroblasts in the development of breast cancer. The main objective is to establish a representative number of primary breast epithelial and fibroblastic cells and investigate the expression and the status of various tumor suppressor and onco-proteins in both tumor cells and their associated fibroblasts.



**FIGURE 3.** Atr controls UV-dependent up-regulation and phosphorylation of p16. Cells were UV-treated (5 Jm<sup>-2</sup>) and reincubated for the indicated periods of time, and then whole cells extracts were subjected to immunoblotting analysis.

### Project description

The major focus of this research project is to gain a deeper understanding of the role of checkpoint proteins such as p53 and p16 in DNA repair of UV-light induced DNA damage, and also to get more insight into the molecular basis of DNA damage induced cell cycle checkpoints and apoptosis.

### Progress

We have shown this year that the carcinogenic UV light up-regulates p16 protein by decreasing its turnover. This induction is neither cell type nor cell cycle-dependent and occurs in response to different UV folquences. Furthermore, the phospho-Serine/Threonine specific antibodies were utilized to show UV-dependent phosphorylation of p16. In addition, it has been shown that caffeine up-regulates p16 protein levels but inhibits its UV-dependent induction. Next, using the ATR-deficient FO2-98 cells and specific ATR siRNA we have shown the implication of the Atr protein kinase in UV-related p16 activation and phosphorylation. Interestingly, Atr is also responsible for the induction of p21<sup>WAF1</sup> in response to UV light, but does not have significant effect on the induction/phosphorylation of p53. Furthermore, we have shown that 40% of primary meningioma cells are defective in UV-related p16 up-regulation.

### Progress

We have characterized 10 primary tumor-associated fibroblasts and have shown that all of them express high levels of survivin, an anti apoptosis cancer biomarker protein. Consequently, most of these cells exhibited high resistance to both UV light and cisplatin. These results indicate that tumor associated fibroblasts display neoplastic-associated changes and therefore have an active role in the development and progression of breast cancer.

### FUTURE RESEARCH DIRECTION

Further characterize the *curcumine* as potential potent anti-medulloblastoma drug. Elucidate the role of breast stromal fibroblasts in the development of breast carcinoma and study the role of curcumin, as nontoxic agent, in inhibiting breast fibroblast-related carcinogenesis. We are also interested in elucidating the role of the tumor suppressor p16 protein in this process. Continue to study the role of the *γ-synuclein* gene in the development and progression of ovarian cancer.

## PUBLICATIONS

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- Huda H. Al-Khalaf, Boleslaw Lach, Ayman Allam, Maher Hassounah, Ahmed AlKhani, Nasser Elkum, Salman A. Alrokayan and Abdelilah Aboussekhra. Expression of survivin and p16(INK4a)/Cdk6/pRB proteins and induction of apoptosis in response to radiation and cisplatin in meningioma cells. (2008). *Brain Res.*, 1188:25-34.
- Zakia Shinwari, Pulicat S. Manogaran, Salman A. Alrokayan, Khaled Al-Hussein and Abdelilah Aboussekhra. Vincristine and lomustine induce apoptosis and p21(WAF1) up-regulation in medulloblastoma and normal human epithelial and fibroblast cells. (2008). *J. Neuro-Oncology*. In Press.

## The Section of

# ENVIRONMENTAL HEALTH

The Environmental Health Section (EHS) continues to maintain its primary goal to assess environmental pollutants that have potential impact on the general population with a particular emphasis on children and women.

During the year 2007, we managed to complete our PSCDR funded project on the relationship between prenatal and postnatal lead exposure and early cognitive development and started a new RAC project in collaboration with King Saud University looking at the impact of dental amalgam in children. We also provide consultation, technical assistance and training. Our major activities during this year are summarized below:

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### **Head:**

**Iman Al-Saleh, PhD**

### **Members:**

Neptune Shinwari

Abdullah Mashhour

Al Anoud Al-Sedairi (MSc student)

Inaam Al-Doush (until 10<sup>th</sup> November  
2007)

## ONGOING RESEARCH PROJECTS

**Project title: "Effects Of Environmental Pollutants Exposure On The Pregnancy Outcome Of Women In Al-Kharj Area". RAC # 2040 017. This project is funded by King Abdulaziz City for Science and Technology (KACST # AT 23-7) with a total fund of SR 393,600.**

This project is in collaboration with King Khalid Hospital, Al-Kharj. The duration of the project is 36 months. We have started the project on 7<sup>th</sup> July 2005.

**Investigators:** Iman Al-Saleh (principal investigator), Mohamed Hassan Gamal El Din and Abdulla Rabah (co-investigators).

### Project description

*In utero* exposures to environmental contaminants can occur through maternal-placental transfer. High level maternal exposures to environmental pollutants, such

as lead, mercury, cadmium, DDT, polycyclic aromatic hydrocarbons and tobacco smoke have been associated with congenital anomalies, severe developmental and cognitive impairment, and growth retardation in offspring. Evidence shows that fetuses and infants are more affected than adults by a variety of environmental pollutants because of differential exposure, physiologic immaturity and a longer lifetime over which diseases initiated in early life can develop. It is clear that the Saudi population, like any other populations, is susceptible to environmental pollutants in spite of the difference in the sources of exposure. Moreover, there have a number of hospital-based studies in different cities in Saudi Arabia, which noted a high prevalence of birth defects, infant mortality and congenital malformations with regional variations in the pattern. This cross-sectional study will examine the potential links between environmental pollutants and the pregnancy outcome of Saudi women living in Al-Kharj district. Prenatal exposure to lead, cadmium, mercury, DDT, polycyclic aromatic hydrocarbons and tobacco smoke will be measured in 1522 umbilical cord, venous blood samples and placental

**TABLE 1.** Descriptive statistics of the data (mean  $\pm$  SD and ranges) of the measured variables.

Analytes	N	Mean + SD	Range
Cord lead levels ( $\mu\text{g}/\text{dL}$ )	1572	2.551 $\pm$ 2.592	0.154-56.511
Maternal lead levels ( $\mu\text{g}/\text{dL}$ )	1577	2.897 $\pm$ 1.851	0.073-25.955
Cord cadmium levels ( $\mu\text{g}/\text{L}$ )	1566	0.780 $\pm$ 0.623	0.245-15.325
Maternal cadmium levels ( $\mu\text{g}/\text{L}$ )	1565	0.986 $\pm$ 0.313	0.233-3.157
Cord mercury levels ( $\mu\text{g}/\text{L}$ )	1561	3.360 $\pm$ 2.666	0.007-26.532
Maternal mercury levels ( $\mu\text{g}/\text{L}$ )	1574	3.014 $\pm$ 6.314	0.002-206.410
Cord p,p-DDE levels ( $\mu\text{g}/\text{L}$ )	1533	0.228 $\pm$ 0.956	0.01-19.950
Maternal p,p-DDE levels ( $\mu\text{g}/\text{L}$ )	1517	0.570 $\pm$ 1.772	0.002-29.110
Cord MDA levels (nmol/mL)	1572	0.981 $\pm$ 2.357	0.002-50.633
Maternal MDA levels (nmol/mL)	1576	4.493 $\pm$ 4.155	0.002-31.755
Cord tail length ( $\mu\text{m}$ )	714	34.637 $\pm$ 8.169	23.07-76.80
Maternal tail length ( $\mu\text{m}$ )	710	36.093 $\pm$ 8.454	24.09-83.65
Cord tail DNA %	715	9.197 $\pm$ 5.560	1.55-40.44
Maternal tail DNA %	711	10.321 $\pm$ 5.52	1.92-45.23
Cord tail moment	715	2.260 $\pm$ 1.952	0.18-14.73
Maternal tail moment	711	2.585 $\pm$ 1.964	0.32-17.02
Urinary cotinine ( $\mu\text{g}/\text{g Cr}$ )	1571	500.637 $\pm$ 7037.192	0.539-202079.133

tissues collected at the time of delivery. Furthermore, urinary cotinine and 1-hydroxypyrene (as a major pyrene metabolite), will be determined in mothers as an indicator of tobacco smoke and individual's internal dose of PAHs respectively. A detailed questionnaire will be administered at birth, which assesses risk of exposure to these pollutants. Pregnancy outcomes evaluation such as incidence of small for gestation (less than tenth percentile of weight for each completed gestational week between 22 and 44 weeks), low birth weight (<2500 g), gestational duration (from the last menstrual period to the termination of pregnancy), fetal death (fetus born 500 g or 22 weeks' gestation with no signs of life), neonatal death (death <28 days of life) and other congenital malformations. A number of studies have emphasized the important role that oxidative DNA damage is playing in various diseases including cancer due to carcinogenic compounds. Peroxidative lipid damage will be determined as malondialdehyde production in the presence of thiobarbituric acid in serum samples. The genotoxic effects of environmental pollutants on the fetus will be evaluated by using comet assay, where the migration of DNA from the center of cells will be measured. It is hoped that findings of this study will help to understand the source of exposure among the studied population and to develop interventions to minimize its impact.

### Progress

During the last year, the following steps were accomplished:

- The completion of cadmium analysis in 3131 cord blood and maternal venous blood samples;
- The completion of mercury analysis in 3135 cord blood and maternal venous blood samples;
- The completion of malonaldehyde (MDA) analysis in 3148 cord blood and maternal venous blood samples;
- The completion of *p,p*-DDT and its metabolites (*p,p*-DDE and *p,p*-DDD) analysis in 3050 cord blood and maternal venous blood samples;
- The completion of lead, cadmium and mercury in 1578 placental tissues;
- Laboratory analysis of polycyclic aromatic hydrocarbons in 1000 cord blood and maternal venous blood samples;
- Laboratory analysis of *p,p*-DDT and its metabolites (*p,p*-DDE and *p,p*-DDD) analysis in 900 placental tissues; and
- Two progress reports were submitted and approved by the King Abdulaziz City for Science & Technology.

### PRELIMINARY RESULTS

**General Characteristics.** A total of 1578 women living in Al-Kharj, agreed to participate in this study between June 2005 and June 2006. Average age of the mothers was  $28.5 \pm 6.0$  year (16–50). The pregnant body mass index (BMI) was  $27.1 \text{ kg/m}^2$ ,  $28.5 \text{ kg/m}^2$  and  $29.2 \text{ kg/m}^2$  during the first, second and third trimesters respectively. The gestational age was 37.9 weeks in the range of 22 to 44 weeks, and the weight of newborns was 3.14 kg. Pregnancy weight gain during the three trimesters was calculated. The average increase in maternal weight during the second trimester was  $2.38 + 3.9 \text{ kg}$  and peaked during the third trimester to  $5.97 + 5.6 \text{ kg}$ .

**Levels of pollutants.** The sample size, means, standard deviations, and the ranges of the lead, cadmium, mercury, *p,p*-DDT, *p,p*-DDE, *p,p*-DDD, MDA, tail moment, tail length and tail DNA in cord and maternal venous blood of women are provided in Table 1. Cotinine in urine samples was measured as a biomarker of cigarette smoking. Urinary cotinine data were expressed in  $\mu\text{g/g Cr}$  in order to correct for the dilution of urine.

**Blood lead results.** Average lead level in maternal venous blood was  $2.897 \pm 1.851 \mu\text{g/dL}$  (0.073–25.955) while this level was  $2.551 \pm 2.592 \mu\text{g/dL}$  (0.154–56.511) in cord blood. The relationship between lead levels in maternal venous and cord blood was found to be statistically significant ( $r=0.463$ ,  $P=0$ ). According to the CDC (1991), the upper limit of tolerable blood lead levels for children should be less than  $10 \mu\text{g/dL}$ . Among all mother and newborns, 0.89% and 0.83% respectively exceeded  $10 \mu\text{g/dL}$  blood lead levels. However, the mean cord and maternal blood lead levels ( $2.551 \mu\text{g/dL}$  and  $2.897 \mu\text{g/dL}$  respectively) was about one-fourth the CDC cutoff level, but the highest lead value of cord blood ( $56.511 \mu\text{g/dL}$ ) was approximately six the CDC cutoff. Regardless of the small proportion of newborns with "high" cord blood lead levels in Al-Kharj, this study suggests that *in utero* lead exposure may be more of a widespread problem in the area and might cause adverse effects on the growth and development in young children even at very low exposure levels.

**Blood cadmium results.** The cadmium concentrations of the 1565 mothers ranged from 0.233 to  $3.157 \mu\text{g/L}$  with a mean value of  $0.986 \pm 0.313 \mu\text{g/L}$ . The corresponding levels of their newborns ranged from 0.245 to  $15.325 \mu\text{g/L}$  with a mean of  $0.780 \pm 0.623$

µg/L. Only 5 newborns had blood cadmium levels <5 µg/L, the OSHA Safety Standard for cadmium (OSHA 2003) but if we use 1 µg/L as the threshold limit of clinical importance, there were 204 newborns (13%). None of the participating women had venous blood cadmium >5 µg/L, whereas 761 (48.6%) had cadmium > 1 µg/L. When the correlation between cadmium in maternal venous and cord blood was analysed, no correlation was found ( $r=0.046$ ;  $P=0.069$ ).

**Blood mercury results.** Mean maternal mercury at delivery was 3.014 µg/L, with a range of 0.002-206.410 µg/L and mean cord mercury was 3.360 µg/L, with a range of 0.007-26.532 µg/L. There were 176 mothers (11.2%) and 203 newborns (13.0%) with mercury levels  $\geq 5.8$  µg/L (the EPA Reference dose) while that is assumed to be without appreciable harm (CDC 2004).

***p,p*-DDE, *p,p*-DDD and *p,p*-DDT results.** *p,p*-DDE was detected in 99.8% of the mothers and 99.1% of the newborns. Sixty-two newborns had *p,p*-DDE  $\geq 1$  µg/L and the concentrations ranged as high as 19.95 µg/L. There were 187 mothers with *p,p*-DDE  $\geq 1$  µg/L and the highest level was 29.11 µg/L. A positive statistically significant association was observed between *p,p*-DDE levels in cord blood and maternal blood ( $r=0.480$ ;  $P=0.0$ ). For the other analytes, *p,p*-DDD was quantified in 6 newborns (out of 1536) and 12 mothers (out of 1516). While *p,p*-DDT was found in 7 newborns and 21 mothers. We will present only the results of *p,p*-DDE.

**Urinary cotinine status.** Urinary cotinine, one of the main metabolites of nicotine, was used as a biomarker for assessment of direct or passive exposure to cigarette smoke. In this study, none of the mothers had zero urinary cotinine. There were 141 women (9.0%) of women had cotinine values  $\geq 30$  µg/g Cr in the range of 30.14 to 202079.13 µg/g Cr, a level commonly associated with household environmental tobacco smoke (ETS) exposure. Around 36 mothers (2.3%) of the tested population with urinary cotinine in the range of  $\geq 50$  to 150 µg/g Cr were truly heavily exposed to ETS while 40 (2.5%) women with urinary cotinine  $\geq 150$  µg/g Cr were most likely smokers. None of the mothers were smokers but 25.8% of them living in household where one or more family members smokes. Among the tested

pollutants, only cord and maternal lead levels were weakly but significantly correlated with urinary cotinine with  $r$  of 0.059 ( $P=0.019$ ) for cord lead and  $r$  of 0.063 ( $P=0.013$ ) for maternal lead.

Although preliminary statistical data analyses using SPSS software was performed for some of the completed data, the results are not conclusive. A number of studies have identified a number of demographic, socioeconomic and environmental factors might affect the pregnancy outcome. Although, a large number of variables were collected in this study, it is premature to include them in the multiple regression analysis because it is necessary to insure data integrity; beforehand, by checking likely errors.

## NEWLY APPROVED PROJECTS

**Project title:** "Saudi Children And Mercury Exposure: The Impact Of Dental Amalgam". RAC# 2070 010.

This is a master research project in collaboration with Department of Zoology, King Saud University. The duration of the project is 12 months. We have started the project on 2nd June 2007.

**Investigators:** Iman Al-Saleh (principal investigator), Al anoud Al-Sudairi (master student) and Ebtessam Al Olyan (co-investigator).

### Project description

Mercury is a common environmental toxin that causes a wide range of adverse health effects in humans. Exposure to mercury typically occurs by inhalation, ingestion or skin absorption. Dental amalgam seems to be the most important source of mercury exposure in Saudi Arabia. It is; widely, used because of its apparent effectiveness against the highly prevalent caries among school children. However, the mounting scientific evidence has shown that exposure to mercury, from dental amalgam or other sources, might have neurological or/and nephrotoxic effects. This has led us to design this comparative study in order to: (1) evaluate the extent of mercury exposure with and without dental amalgam; and (2) investigate its health effects. We hope that results of this study

will provide scientific evidence on the health effect of dental amalgam on children that could contribute to improve professional knowledge, awareness and public health policy.

### Progress

Since 4<sup>th</sup> of July 2007, 444 urine, hair and nail samples were collected from 148 children between the ages of 6 to 12 years old; who met our inclusion criteria. The project is progressing very smoothly and we will hopefully manage to reach our target sample size of 200 children according to plan.

### CORE SERVICE ACTIVITIES

#### Service-for-fee activities

- Analysis of paclobutrazol in mango samples to the Ministry of Agriculture, Jizan.
- Analysis of lead and mercury in cosmetics samples to the Saudi Food & Drug Authorities.

### FUTURE RESEARCH DIRECTION

The EHS will continue working on our existing and newly approved projects. The King Abdulaziz City for Science and Technology has provided us with a fund of SR75,000 to conduct the following research project "*Determination of phthalates in drinking water, juices and milk packed in locally manufactured plastic bottles*". The overall aim of this project is to analyze ten (10) widely consumed brands of bottled milk, juices and drinking water samples that are manufactured locally for five of the most widely

used phthalates as plasticizers in PVC to determine their potential risk to human health or the environment. The data obtained by this work will help to estimate exposure of the local population to phthalates and contribute to the development of effective measures to reduce the exposure.

### PUBLICATIONS

- Al-Saleh I, Billedo G, Shinwari N. Serum malonyldialdehyde levels in Saudi population and its relationship to a number of factors such as age, gender, antioxidant levels and health status. *Trace Elements and Electrolytes* 2007; 24(2): 103-111.
- Al-Saleh I. Potential impact of DDT and its metabolites on health. . In: *Air Pollution: New Research*, ed. Livengston, JV. *Nova Science Publishers, Inc.* 2007, pp.99-126.
- Al-Saleh I , El-Doush I, Billedo G, , Mohammed G, Yosef G. Selenium and vitamins status in Al-Kharj district, Saudi Arabia and its possible relationship with common endemic diseases. *Journal of Environmental Pathology, Toxicology and Oncology* 2007; 26(3): 221-243.
- Al-Saleh I, El-Doush I, Billedo G. Age and gender-related reference values for serum dl- $\alpha$ -tocopherol and all-trans-retinol levels in Saudi population. *International Journal for Vitamin and Nutrition Research* 2007; 77(5): 326-335.
- Al-Saleh I, Coskun S, Mashhour A, Shinwari N, El-Doush I, Billedo G, Jaroudi K, Al-Shahrani A, Mohamed G. Exposure to heavy metals (lead, cadmium and mercury) and its effect on the outcome of in-vitro fertilization treatment. *International Journal of Hygiene & Environmental Health* 2007; 210(6): .



## Research Unit

# LASER MEDICINE

*L*ow Power Laser Therapy (LPLT) is recognized worldwide for its importance in Dentistry, Dermatology, Immunology, Neuroscience, Oncology, Rheumatology and Physical Therapy.

LPLT may be applied for immediate relief from acute and chronic pain, for treatments of inflammatory conditions, nerve and bone regeneration and for the promotion of wound and burn healing for diabetic patients among others. Photodynamic Therapy (PDT) is an essential Laser Application for local malignancy selectively eradicating tumors with the help of photosensitizers.

The rapid advancement of Phototherapy in wound, burn, pain management, PDT etc. and its instrumentations kept the biologist engaged in validating claims of efficacy and the establishment of optimal dosimetry.

During the past two decades our laboratory had been engaged in laser wound and burn healing biostimulation and photodynamic therapy studies filling up gaps of knowledge demonstrating the ability of various laser wavelengths to affect bio-modulation in a dose dependent manner and the establishment of efficient laser clinical dosimetry.

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### **Head:**

**Farouk A.H. Al-Watban, MSc., PhD, FASLMS**

### **Members:**

Xing Yang Zhang, MD

Bernard L. Andres, RMT (AMT)

Azizah A. Al-Anazi, BSc (Biochem)

Maria Cecilia Perez

**RESEARCH PROJECTS**

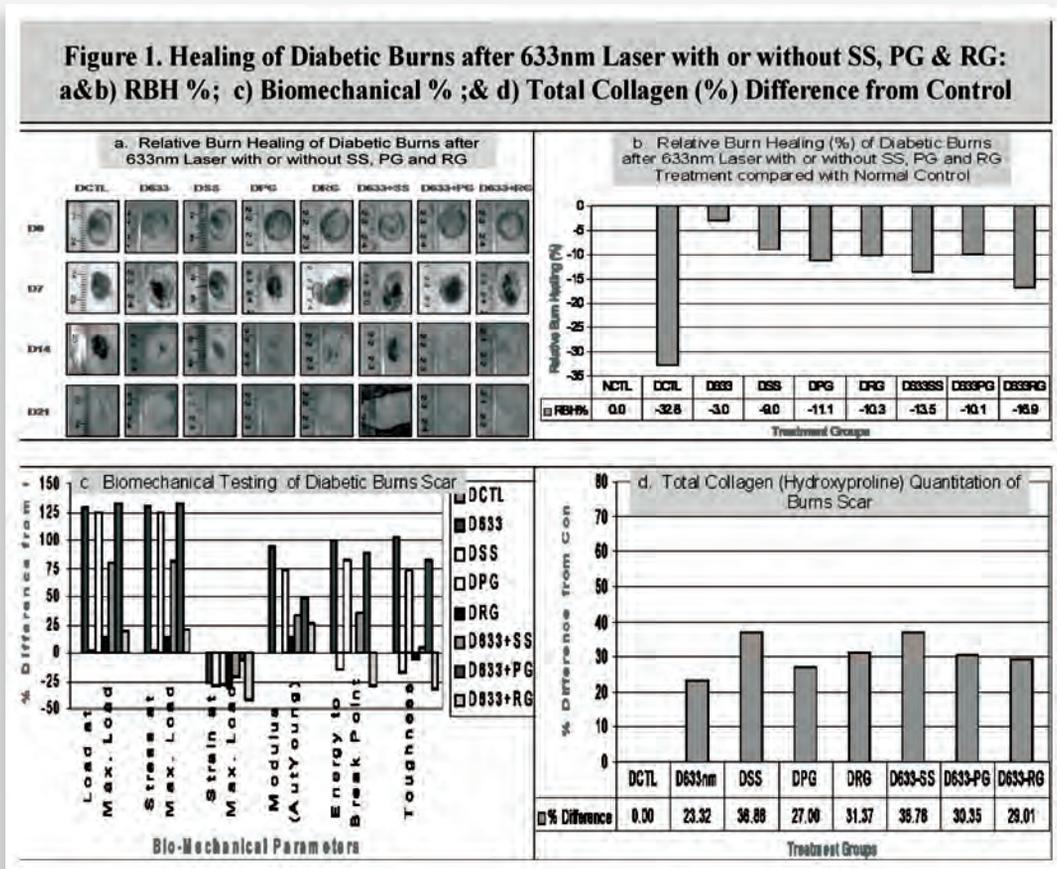
**Project Title: (#2020002) Photo-Biostimulation: Laser Effect in Wound Healing of Diabetic and Non Diabetic Rats**

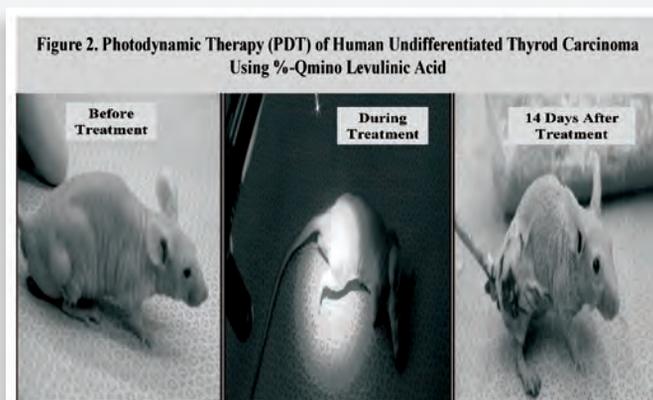
**Investigator:** Dr. Farouk A.H. Al-Watban, MSc, PhD, FASLMS

**Project description**

Wound healing is a natural response of the body after

tissue injury. Every wound initiates mechanisms that are designed to restore tissue integrity through formation of new structures that more or less resembles and matches the original function. Wound healing is not restricted locally to the regeneration process but also to a high degree determined by the overall condition of an animal, which again depends on diverse endogenous factors such as age, nutrition, immunologic status, metabolic condition or the overall health status of the animal. The complex relationship between the wound and the experimental animal is highlighted when the healing is impaired so that the therapy that is initiated would be integral to its condition.





Our study with the use of four wound healing models: non-diabetic wound; diabetic wound; non-diabetic burn; and diabetic burn was designed to explore the utility of phototherapy given the specific health condition of the animal and the type of tissue injury. This is further advanced by comparing the efficacy of phototherapy with wound healing drugs and to determine whether synergy is exhibited by the best laser wavelength with pharmaceutical agents. Three major parameters were used in determining efficacy: 1) Relative Wound/Burn Healing %; 2) Collagen Concentration (Difference from Control %) and 3) Tensile Strength (Difference from Control %).

#### Specifically, our goals are to

- Determine the effects of several Low Power Laser (LPL) GaAs Diode-Lasers 532nm, 633nm, 670nm, 785nm, 810nm and 980nm on wound/burn healing in the non-diabetic and diabetic rats.
- Explore the use of low power from the widely used high power (HPL) surgical lasers, e.g. Nd: YAG (1060nm), Er: YAG (2940nm), CO<sub>2</sub> (10600nm), and excimer lasers for biomodulation.
- Use Polychromatic light emitting diode (LED) as new light source in wound healing
- Determine the efficiency of laser biostimulation using IR and UV then compare it with wound healing drugs Solcoseryl (SS), Regranex (RG) and Polygen (PG).
- Determine whether a synergistic or additive effect exists in varying the drug dose and laser dose combinations.

- Biomechanical and Biochemical Testing of Scars after various Laser/LED and Drug treatments.

#### Progress

This project is externally funded by KACST. Various abstracts and manuscripts have been presented and published.

**Project title: (# 960002): Laser Biostimulation: Wound Healing**

**Investigator:** Farouk A.H. Al-Watban, MSc, PhD, FASLMS

#### Project description

Laser Therapy is a biological phenomenon generated from low power laser (LPL) photons eliciting non-thermal photochemical conversion of absorbed energy. The photochemical conversion of absorbed energy effects biomodulation on the tissue that is a new, safe, and effective treatment for a multitude of soft tissue conditions. LPLT may be applied for immediate relief of acute and chronic pain, for treatments of inflammatory conditions, nerve and bone regeneration and for the promotion of wound healing. *In-vitro* and *In-vivo* models were used for Laser Biostimulation studies.

#### Progress

Several *in-vivo/in-vitro* abstracts and full manuscripts have been published.

## FUTURE RESEARCH DIRECTION

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The Laser Medicine Research is rapidly advancing with the incessant innovations in laser technology. The clinical and diagnostic applications of lasers in medicine are exciting areas that have continued to evolve and improve. The commissioning of the "cutting edge" technology of the 21<sup>st</sup> century is being realized only with the conduct of research.

The Laser Medicine Research Section continues to achieve its goal in advancing the use of lasers in medical treatment, which has expanded exponentially despite the cost of high-technology lasers. The development of small, less expensive and more convenient laser sources runs parallel with clinical research to better understand the diagnostic and therapeutic values of the different laser wavelengths. Thus, the laser continues to be an important tool in clinical patient care and of the application of laser in the new millennium for the benefit of human kind.

We aim to contribute pertinent evidence regarding the effects of low power lasers and LED in PDT, as well as, in tissue repair processes of wounds and burn injuries using non-diabetic and diabetic animal models with eventual application of the optimum dosimetries in clinical trials.

## PUBLICATIONS

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### Full Manuscripts

- F.A.H. Al-Watban, X.Y Zhang (2005 Paper). "Photodynamic Therapy of Human Undifferentiated Thyroid Carcinoma Bearing Nude Mice Using Topical 5-Aminolevulinic Acid", *Journal of Photomedicine and Laser Surgery*, Vol. 23, No. 2: Pp. 206-211.
- F.A.H. Al-Watban, G. Delgado (2005 Paper) "Burn healing with a Diode Laser, 670 nm at Different Doses as Compared to a Placebo Group" *Journal of Photomedicine and Laser Surgery*, Vol. 23, No. 3, Pp.: 245-250.
- F.A.H. Al-Watban, B.L. Andres (2006 Paper). "Polychromatic LED in Oval Full-Thickness Wound Healing in the Non-diabetic and Diabetic Rat", *Journal of Photomedicine and Laser Surgery*, Vol. 24, No. 1, Pp10-16.
- F.A.H. Al-Watban, X.Y. Zhang, B.L. Andres (2006 Paper). "Low Power Laser Therapy Enhance Wound Healing on Diabetic Rats Comparing Different Lasers", *Journal of Photomedicine and Laser Surgery* (PMLS), Vol. 25, No. 2, Pp, 72-77.
- F.A.H. Al-Watban, B.L. Andres (2006 Paper). "Low Power Laser Therapy: Photo-biostimulation For Patients with Post-operative Acute Wound and Burns", submitted to Touch Briefings.com for *US Dermatology Review*.
- F.A.H. Al-Watban, B.L. Andres (2007 Paper). "The Dosimetric Extrapolation of Low Power Laser Therapy from Animals to Humans for Diabetic Wound and Burn Healing", Proceedings of the 6th International Congress of World Association for Laser Therapy (WALT-2006), Limassol, Cyprus, 25-28 October, *Journal of Photomedicine and Laser Surgery* (PMLS) Vol. 25 No. 4, 2007, Abstract # 39, p. 328.
- F. A.H. Al-Watban, B. L. Andres (2007 Paper) "Low Power Laser Therapy for Wound and Burn Healing", submitted to *Arab Health* on October 2007.

### Abstracts

- A.A.B. Al-Anize, B.L. Andres, F.A.H. Al-Watban, (2007 Abstract). "Low Power Laser Therapy", Proceedings of the 6<sup>th</sup> International Congress of World Association for Laser Therapy (WALT-2006), Limassol, Cyprus, 25-28 October, *Photomedicine & Laser Surgery Journal* (PMLS) Vol. 25 No. 4, 2007, Abstract # 39, p. 329.
- X.Y. Zhang, B.L. Andres, F.A.H. Al-Watban (2007 Abstract). "The Effect of Photodynamic Therapy Using Topical 5-Aminolevulinic Acid in Treating Human Undifferentiated Thyroid Carcinoma on Nude Mice", Proceedings of the 6th International Congress of World Association for Laser Therapy (WALT-2006), Limassol, Cyprus, 25-28 October, *Photomedicine & Laser Surgery Journal* (PMLS) Vol. 25 No. 4, 2007, Abstract # 39, p. 329.
- B.L. Andres, F.A.H. Al-Watban (2007 Abstract). "Wound and Burn Healing Therapy Using LED in Normal and Diabetic Models: Biomechanical and Biochemical Analysis of Scar", Proceedings of the 6<sup>th</sup> International Congress of World Association for Laser Therapy (WALT-2006), Limassol, Cyprus, 25-28 October, *Photomedicine & Laser Surgery Journal* (PMLS) Vol. 25 No. 4 2007, Abstract # 39, p. 330.
- F.A.H. Al-Watban, B.L. Andres, X.Y Zhang, A.A. Al-Anazi (2007 Abstract). "Low Power Laser and LED Therapy of Mid-Dermal Burns in the Normal & Diabetic Rats", Proceedings of the 12<sup>th</sup> International Congress of the European Medical Association (EMLA) in conjunction with the World Association of Laser

Therapy (WALT), European Laser Association (ELA) and Czech Society for Use of Laser in Medicine (CSULM-CLS JEP) Prague, Czechoslovakia, 20-22 September 2007, p. 39.

- F.A.H. Al-Watban, B.L. Andres, X.Y Zhang (2007 Abstract). "Cosmetic Effect of Laser Therapy as a Wound & Burn Healer" presented at the 3rd Congress of European Masters in Aesthetic & Anti-Ageing Medicine (EMAA)-The Practical Congress, Paris, France, 12-14 October 2007.
- F.A.H. Al-Watban, B.L. Andres, X.Y Zhang, A.A. Al-Anazi (2007 Abstract). "Low Power Laser and LED Therapy of Mid-Dermal Burns in the Normal & Diabetic Rats", presented at the 17<sup>th</sup> ISLMS and 22nd IALMS International Congress Laser Medicine w/ Pre-Conference Courses Laser Florence 2007. Florence, Italy, 8-10 November 2007.

#### Other Activities

The establishment of the "World Academy for Laser Applications" (WALA) and its website: [www.laser-wala.com](http://www.laser-wala.com).

The World Association for Laser Applications, a non-profit organization was conceptualized in 2004 and established in 2007 to pursue the promotion of Research, Education and Clinical Applications of Laser Photo Stimulation, and to serve as catalyst in developing a regional hub for Photonics-Optoelectronic Industries in the GCC Countries, its neighbors including the Far East.

#### Immediate goals

- To support Medical Professionals, Engineers, Scientists and End-Users of Laser Technology for training, Education, Research and Technical aspects of this rapidly advancing industry.
- To collaborate with manufacturers and end-users for systems and product development.
- To serve as an agency aiding in certification programs for laser professionals; Laser Safety Officers and Laser Operators.
- To serve as one stop resource centre for continuous education, year round local and international seminars, workshops and symposia.

#### Long term goals

- To encourage relocation of selected photonics/ opto-electronics industries in the GCC Countries as

partners in application based development of laser systems.

- To organize and conduct laser product expositions as a strategy for market expansion and to foster cooperation.

#### WALA activities during 2007

- "The Laser Energy Concepts & Safety Regulations Training course for Medical Professionals", Sept. 2-5, 2007 Sheraton Hotel, Manama, Bahrain, organized by WALA (World Academy for Laser Applications) in cooperation with Elegant Training.
- Proctored 21 examinees for Medical Laser Safety Officer (MLSO), Aesthetic Laser Operator (ALO) and Surgical Laser Operator (SLO) Certifications.

#### Peer-Reviewer

- "A Study to Evaluate the Effects of Low Level Laser Therapy (LLL) on Dermal and Adipose Stem Cells". Reviewed & returned to MD Jenkins, Research Administration Division, *The Medical Research Council*, Tygerberg, South Africa.
- "Low Energy Helium-Neon Laser Ensures Knee Cartilage Repair: An Experimental Short-term Assay in Rabbits", reviewed and returned March 03, 2007 to Anja Selna of the *Journal of Laser Application*.
- "Effect of Low-Level Laser Therapy on Mast Cell Number and Degranulation in Deep Second-degree Burn of Rats", reviewed & returned to Carolyn Gibson to the *Photomedicine and Laser Surgery* on March 26, 2007.
- "Influence of Laser Photobiomodulation Upon Connective Tissue Remodelling During Wound Healing", reviewed & returned on November 28, 2007 to D. Robinson of the *Journal of Photochemistry and Photobiology B: Biology*.

#### Commendable Achievements

- Dr. Farouk A.H. Al-Watban, MSc, PhD, FASLMS, is currently the President of World Association for Laser Therapy (WALT) from 2006-2008.
- Dr. Farouk A.H. Al-Watban, MSc, PhD, FASLMS, is also the Founding-President of World Academy for Laser Applications (WALA) in 2007 with an initial course offering held in Bahrain, and the proctoring of certification examinations for Laser Safety Officers (LSO), Aesthetic Laser Operator (ALO) and Surgical Laser Operator (SLO) Certifications.



## Research Unit

# MOLECULAR VIROLOGY AND INFECTIOUS DISEASES

Despite outstanding advances in medical research and treatments nowadays, infectious diseases remain among the leading causes of death worldwide and Saudi Arabia is no exception. This is attributed to the following: (1) emergence of new infectious diseases; (2) re-emergence of old infectious diseases; and (3) persistence of intractable infectious diseases. Changes in human demographics, behavior, land use, travel etc. are contributing to new disease emergence by changing transmission dynamics and bringing people into more frequent contact with pathogens.

The Molecular Virology and Infectious Diseases (MVID) unit concentrates on studying the distribution and prevalence of infectious agents in the Kingdom. Molecular techniques are employed to study viral and bacterial genomic variations and genotypes. Our major effort in this direction was on human diarrhea viruses, and other bacteria that cause nosocomial infections including *Acinetobacter sp.*, vancomycin-resistant *enterococci*, and methicillin-resistant *Staphylococcus aureus*. Other projects include the development of computational tools for the analysis of DNA sequences to study phylogenetic relationship between infectious organisms and the relationship between disease status and infectious organisms.

The Section was also involved in various projects that would share information from Saudi Arabia with the global scientific community on hepatitis B virus genotypes, molecular detection of viruses among drug users, and the occurrence of human herpesvirus type 8 (HHV-8 or KSHV) in various cancer patients and blood donors. Another major focus of the unit is to study host-pathogen interaction and this is represented by studying the effect of various infectious agents on the biology of their host cells.

Also, the section is also collaborating with other scholars and physicians on various projects on detection and pathogenesis of infectious diseases.

### Head:

**Ahmed A. S. Al-Qahtani, PhD**

### Members:

Mohammed N. Al-Ahdal, PhD  
 Alwaleed Alaidan, PhD  
 Abdulrahman Al-Suwaine  
 Ayman Abdelhamed, PhD  
 Maha A. Al-Mozaini, PhD  
 Suhair Abu-Zaid, MSc  
 Marie Fe Bohol, BS  
 Damian Dela Cruz, DVM  
 Hamsa T. Tayeb  
 Hanan Shaarawi

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## SPECIAL ACCOMPLISHMENTS

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The contribution of this Section (Dr Al-Ahdal as Chairman of Biosimilars Guidelines Committee) in establishing Drug Master File Requirements for the Registration of Biosimilar Drugs as part of the collaboration with the Saudi Food and Drug Authority.

- Continue to use molecular methods for tracing nosocomial pathogens in our hospital and other hospitals inside and outside Riyadh.
- Standardization of molecular diagnostic methods for detection of pathogens in various clinical samples.
- Studying host-pathogen interaction and pathogenesis at the molecular level. This was done by studying Epstein-Bar virus (EBV) and *Leishmania major* and some of the mechanisms involved in their interactions with host cells.
- Collaborate with various Saudi Universities in the Supervision of graduate students.
- Training of students on molecular techniques in microbiology.
- Approval of funding by KACST on three projects presented by scientists in the unit. The projects are as follows:

**1. The First Production of Highly Thermostable Lipase from *Thermophilic Bacterium* Isolated from Saudi Soil: Gene Cloning, Overexpression and Industrial Application to The Asymmetric Access to Enantiomerically Pure Pharmaceuticals and Related Biologically Active Compounds.**

**Principal Investigator:** Mohammed Al-Ahdal, PhD  
**Co-Investigators:** Alwaleed Al-Aidan, PhD and Ashraf Ghanem, PhD  
**Fund:** 2,400,000 Saudi Riyals.

**2. Host Genetic Polymorphism In Toll-Like Receptors And Disease Outcome In Hepatitis B And C Virus-Infected Saudi Patients.**

**Principal Investigator:** Ahmed Al-Qahtani, PhD (MVID)  
**Co-Investigators:** Mohammed Al-Ahdal, PhD (MVID), Ayman Abdelhamed, PhD (MVID), Dr. Khaled Al-Kahtani (Internal Medicine, KFSHRC), Dr. Hamad Al-Ashgar (Internal Medicine, KFSHRC), Dr. Ayman Abduh (KSU)  
**Fund:** 960,000 Saudi Riyals.

## 3. Emergence of Nucleoside Analogs-Resistant HBV.

**Principal Investigator:** Ayman Abdelhamed, PhD (MVID)

**Co-Investigators:** Mohammed Al-Ahdal, PhD (MVID), Ahmed Al-Qahtani, PhD (MVID), Dr. Khaled Al-Kahtani (Internal Medicine, KFSHRC), Dr. Hamad Al-Ashgar (Internal Medicine, KFSHRC), Dr. Ayman Abduh (KSU)

**Fund:** 838,000 Saudi Riyals.

- Maha Al-Mozaini, Research Assistant at the unit, obtained her PhD from The University of London, UK.

## RESEARCH PROJECTS

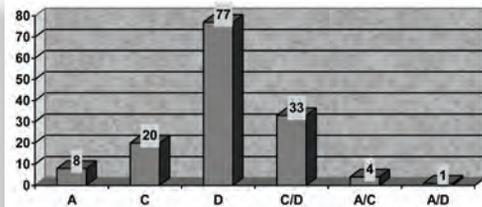
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**Project title: Hepatitis B Virus (HBV) Genotypes Among HBV Surface Antigen Positive Patients.**

**Investigators:** Mohammed N. Al-Ahdal, Damian Dela Cruz, Mohamed Rezeig, Ahmed Hassan, Ahmed Al-Qahtani

### Project description

This project was conducted to identify HBV genotypes prevalent in Saudi Arabia. In many investigations carried out for the prevalence of hepatitis B infections, no extensive studies were done to classify these isolates to determine the genotype. However genotype D is pandemic, but predominant in the Middle East. In this study we identified C/D hybrid and other mixed genotype using reverse hybridization technique that can identify simultaneously mixed genotype present in one sample. Recombination of different genotypes has been reported in many countries. 214 patients were involved for HBV screening by Polymerase Chain Reaction (PCR) of which 137 found to be positive by this test. These positive samples were then subjected for genotyping. The result of the test indicates genotype D is more prevalent in Saudi Arabia; however recombination of two genotypes in one sample is alarming as genotypes plays an important role in HBV treatment and clinical as well as epidemiological implications. More detailed epidemiological studies of hepatitis B virus infection are needed to gain more insight into possible type/subtype-specific pathogenesis in the different regions in the Kingdom as well as the distribution of the genotypes in the various localities.



**FIGURE 1.** Result of genotyping hepatitis B (HBV) by Reverse Hybridization

**Progress**

Completed.

**Project title: Molecular Detection Of Viruses Among Saudi Drug Users.**

**Investigators:** Mohammed N. Al-Ahdal, Alhussain J. Alzahrani, Damian Dela Cruz, Ahmed Al-Qahtani (a collaborative project with the Department of Microbiology, College of Medicine, King Faisal University, Dammam)

**Project description**

This project aims to identify viruses (other than HIV) than are found in the blood of Saudi intravenous (IV) drug users. Eight viruses (HBV, HCV, HDV, TTV, HHV-4, HHV-5, HHV-6, and Parvovirus B19) were screened in 344 serum specimens of HIV-negative IV drug users by PCR. Four of them (HDV, HHV-5, HHV-6, and Parvovirus B19) were never found. The other four were detected,

with TTV being the highest percentages, followed by HCV, HBV and EBV.

**Project title: Human herpesvirus Type 8 (HHV-8) Occurrence Among Cancer Patients, HCV-Positive Patients, Hemodialysis Patients, And Healthy Blood Donors.**

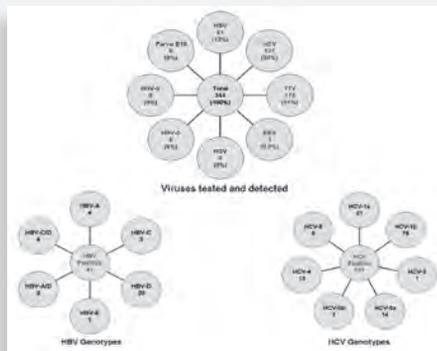
**Investigators:** Mohammed N. Al-Ahdal, Marie F. Bohol, and Ahmed Al-Qahtani

**Project description:**

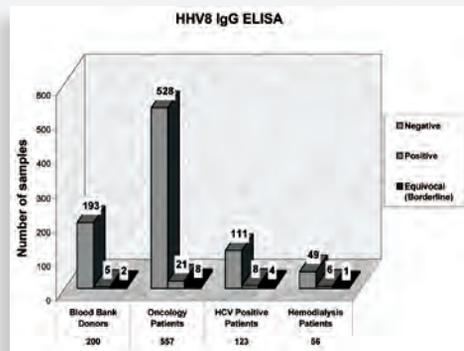
HHV-8 (also known as Kaposi's Sarcoma associated herpesvirus, KSHV) is reported to be present in normal individuals, as well as patients with various conditions, including those with Kaposi sarcomas. The aim of this study is to examine the occurrence of the virus in healthy persons and in patients with various conditions. It also aims to characterize the virus isolates molecularly and elucidate any possible disease association. Viral detection in specimens from blood donors, various oncology patients, HCV positive patients and hemodialysis patients was performed using HHV-8 specific immunoglobulin G antibody ELISA; the assay is made from a whole virus extract, derived from sucrose gradient purified HHV-8 virions isolated from the KS-1 cell line. PCR-RFLP analysis of four ORF of viral genome is in progress.

**Progress**

To be continued.



**FIGURE 2.** Prevalence of viruses in some Saudi drug users.



**FIGURE 3.** Prevalence of HHV-8 in the groups tested in this study.

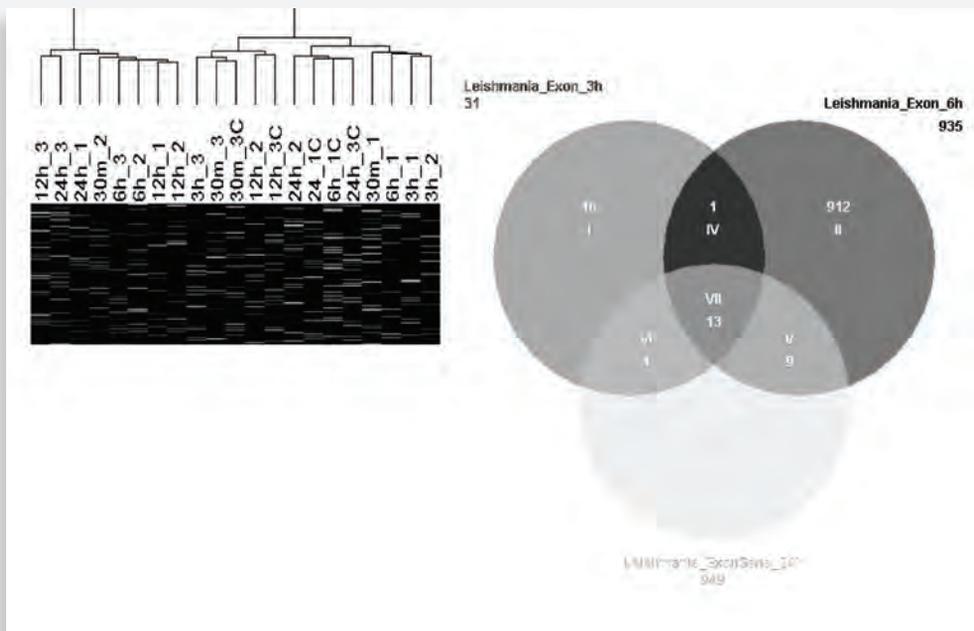
**Project title: Comparison Of Genetic Changes In Transitional And Squamous Bilharzial-Related Bladder Cancer Using Fluorescence In Situ Hybridization.**

**Investigators:** Al-Gahtani, Ahmed and Magdy Aly

**Project description**

Two types of bladder cancer, squamous cell (SC) and transitional cell (TC) differ in their histopathology, clinical outcome and etiology. Therefore, the underlying genetic effects of these two types of tumor may also be different. We compared numerical aberrations of different chromosomes in bilharzial-associated squamous and transitional cell carcinoma of the bladder, and correlated the findings to p53 gene amplification. Cystectomy for invasive bladder was performed in 35 men and 15 women with a mean age of 54.6 years (range 28 to 82). Of these patients 33% had histologically verified squamous cell carcinoma, and 17% had transitional cell carcinoma.

We used fluorescence in situ hybridization to evaluate the numerical aberrations of chromosomes 7, 9 and 17, and alterations in p53. Our results demonstrated that aberrations of chromosome 7 were observed in 75% of the squamous cell carcinoma and in 93% of transitional cell carcinoma. Aberrations of chromosome 9 were also observed in 90% of squamous cell carcinoma, however, they were seen only in 51% of transitional cell carcinoma. Aberrations of chromosome 17 were detected in only 25% of squamous cell carcinoma, compared to 82% in transitional cell carcinoma. The p53 overexpression was similar in both types with 84% for squamous cell carcinoma, and 73% for transitional cell carcinoma. Our data clearly show difference between chromosomal patterns of invasive bilharzial squamous cell carcinoma and transitional cell carcinoma. However, overexpression of p53 in both types was similar. Additionally, aberrations of chromosome 9 were observed in both types, which confirm the 2 pathways in the oncogenesis of squamous cell and transitional cell carcinoma.



**FIGURE 4.** Exon microarray analysis of the transcriptome of THP-1 macrophage cells infected with *L. major*.

### Progress

Completed.

**Project title:** Exon Microarray Analysis Of Macrophages Infected With The Human Protozoan Parasite *Leishmania Major*.

**Investigators:** Al-Qahtani, Ahmed, Mehmet Inan, Maha Al-Amer, Ebtesam Al-Olayan

**Project description:** (ORA proposal 2060023)

Several species belonging to the genus *Leishmania* are of extreme human health importance. They cause a wide range of debilitating diseases ranging from disfiguring cutaneous to the more serious visceral leishmaniasis. *Leishmania* parasitizes on macrophages and in order to create an environment that supports its continuous growth, the parasite must survive the antimicrobial mechanisms that macrophages possess. In this project, we analyzed the macrophage gene expression activity after infection with *L. major*, the causative agent of the cutaneous form of leishmaniasis. We have run a total of 21 samples at 5 different time points in order to determine the real-time gene expression changes at the exon level by using Affymetrix exon array which contains more than 1.4 million probes for the whole human transcriptome. We observed that there are 949 genes are differentially expressed when we compare 24 hours treatment with non treated cells. Six-hour treatment reveals 935 genes are differentially expressed compared with control. We have also identified 13 genes to be common regulatory network between the three time points. The latter genes are selected for further analysis to be used as markers in *Leishmania* infection.

### Progress

To be continued.

**Project title:** Detection of Hepatitis B Virus (HBV) DNA from Saliva by Nested Polymerase Chain Reaction.

**Investigators:** Ahmed Ali Al-Qahtani, Mohammed N. Al-Ahdal, Damian M. dela Cruz, M. Sultan.

### Project description

It is hypothesized that HBV could be transmitted through saliva, epidemiological studies, however, suggest that the infective capacity of HBV viral particles in saliva is low. The purpose of this study is to detect HBV DNA by

using nested PCR with primers specific to core, X-gene and surface gene. Eighty eight saliva samples from HBsAG-positive individuals were tested for the presence of HBV DNA. The data illustrate the diagnostic value of saliva and point to possible role of saliva as a source of HBV infection. In the overall test results, 18 (20%), 28 (32%) and 36 (41%) samples are positive for pre-S, X, and core genes, respectively (Table 2). Therefore, we conclude that HBV DNA can be detected in saliva and primers for the core gene are the most optimum primers for such analysis.

**TABLE 1.** Detection of HBV DNA from saliva samples.

Pre-S gene	18 (20%)
X-Gene	28 (32%)
Core Gene	36 (41%)

### Progress

To be continued.

**Project title:** The First Production of Highly Thermostable Lipase from Thermophilic Bacterium Isolated from Saudi Soil: Gene Cloning, Overexpression and Industrial Application to The Asymmetric Access to Enantiomerically Pure Pharmaceuticals and Related Biologically Active Compounds

**Investigators:** Ashraf Ghanem, Alwaleed Alaidan, Mohammed Al-Ahdal

### Project description

In the present work, emphasis has been imposed to use thermophilic bacteria extracted from Saudi soil (having very high temperature in summer) as a source of thermostable lipase/esterase enzymes. These enzymes have wide biotechnological potential, ranging from their use as additives in laundry detergents to stereospecific biocatalysis. It is anticipated to characterize gene(s) responsible for the production of lipase/esterase on molecular basis. These enzymes will be used in new industrial applications consisting of the enantioselective access to enantiomerically pure pharmaceuticals and related biologically active compounds.

### Progress

To be continued.

**Project title: Direct Enantioselective HPLC Monitoring of Lipase-Catalyzed Kinetic Resolution of Tiaprofenic Acid in Nonstandard HPLC Organic Solvents.**

**Investigators:** Ashraf Ghanem, Alwaleed Alaidan, Mohammed N. Al-Ahdal

**Project description**

The first straightforward lipase-catalyzed enantioselective access to enantiomerically enriched tiaprofenic acid as a versatile method in chiral separation of racemates is demonstrated. The latter was directly monitored by enantioselective HPLC using a 3,5-dimethylphenylcarbamate derivative of cellulose-based chiral stationary phase namely Chiralpak IB (the immobilized version of Chiralcel OD). Nonstandard HPLC organic solvents were used as diluent to dissolve the "difficult to dissolve" enzyme substrate (the acid) and as eluent for the simultaneous enantioselective HPLC baseline separation of both substrate and product in one run without any further derivatization. The existence of a nonstandard HPLC organic solvent (e.g., methyl tert-butyl ether) in the mobile phase composition is mandatory to accomplish the simultaneous enantioselective HPLC baseline separation of both substrate and product. Chirality.

**Progress**

Completed.

**Project title: Molecular Typing of Multiresistant Isolates of *Acinetobacter Baumannii*. ORA Proposal #2060031**

**Investigators:** Alwaleed Alaidan, Buthainah Al-Shahrani, Marie F. Bohol, Abdulrahman Al-Suwaine, Ahmed Al-Qahtani, Mohammed N. Al-Ahdal

**Project description**

*Acinetobacter baumannii* is an important opportunistic pathogen rapidly evolving toward multidrug resistance and is involved in various nosocomial infections that are often severe. Different genotypic and phenotypic procedures were evaluated for the characterization of clinical isolates of *A. baumannii*. However, no generally accepted typing scheme exists. The aims of this study are to find the most suitable methods to discriminate *A. baumannii* clinical isolates, to investigate the clonal distribution of *A. baumannii*, to obtain data on the diversity of clinical isolates of *A. baumannii*, and to determine whether or not the increasing appearance of resistant *A. baumannii*

is due to the spread of an epidemic strains.

**Progress**

Practical work completed.

**Project title: Rapid Pulsed-Field Gel Electrophoresis (PFGE) Protocol for Typing *Serratia Marcescens***

**Investigators:** Alwaleed Alaidan, Marie F. Bohol, Ahmed Al-Qahtani

**Project description**

*Serratia marcescens* causes many diseases, such as urinary and respiratory tract infections, bacteremia, conjunctivitis, endocarditis, meningitis and wound infections. Among molecular typing methods, Pulsed-Field Gel Electrophoresis (PFGE) of genomic DNA is generally considered to be the "gold standard" because of its high discriminating power and it has been successfully used for epidemiological purposes. The main problem of this method is that the preparation of DNA is time-consuming procedure. Moreover, using different protocols to prepare DNA, restriction digestion, and electrophoretic separation of DNA fragments generally makes difficult to interpret and compare the data generated. We submit here a relatively rapid and simple method for typing of *Serratia marcescens* for epidemiological purposes.

In this method, we reduced incubation time for cell lysis and proteinase K treatment to the bacterial cell suspensions prepared directly from agar plates; and shortened washing times by using preheated sterile water and TE buffer. So, the whole genomic DNA was prepared for restriction enzyme digestion within 9 hours depending on the number of the isolates tested. After restriction enzyme digestion with Spe1 for 4 hours, we applied electrophoresis with CHEF-DRIII for 22 hours. The results can be obtained within 36-48 hours using our protocol, allowing to timely evaluation of clinical *Serratia marcescens*.

**Progress**

To be continued.

**Project title: Microevolution In Genomic Short Sequence Repeats Of *Candida Albicans* In Non-Neutropenic Patients.**

**Investigators:** Alwaleed Alaidan, Mohammed. Al-Ahdal, van Belkum A

### Project description

The genome of the yeast *Candida albicans* harbours many genomic short sequence repeats (SSRs). These are stable upon transition of colonization to infection in immune-compromised patients. We show here that in non-neutropenic patients this transition may coincide with variation in several of the SSRs. This may have implications for stage-specific expression of *C. albicans* pathogenicity factors

### Progress

Completed.

### Project title: Analysis of Tn1546 Elements within Vancomycin Resistant *Enterococcus faecium*

**Investigators:** Alwaleed Alaidan, John Hays

### Project description

Enterococci are found in both environment and hospital settings, frequently expressing glycopeptide / high-level aminoglycoside resistance. In recent years, a clonal complex of *Enterococcus faecium* isolates (CC17) has become more prevalent in facilitating global nosocomial-related infection. Currently, no data is available regarding the position of clinical *E. faecium* isolates from the Middle East within the global context. Therefore, we investigated 34 Saudi Arabian VanA type vancomycin resistant *Enterococcus faecium* isolates with respect to genotype, antibiotic susceptibility patterns, the presence of enterococcal surface protein (*esp*) and hyaluronidase (*hyl*) genes, characterization of Tn1546 elements, and transformation efficiencies. PFGE and MLST analysis revealed the presence of 31 and 6 different genotypes, respectively. Further, 3 new ST types were determined. Ninety seven percent (33/34) of isolates were associated with clonal complex 17, with all isolates being resistant to ampicillin and sensitive to linezolid. The *esp* and *hyl* genes were found in 44% (15/34) and 53% (18/34) of isolates, respectively.

### Progress

To be continued.

### Project title: Genotyping of Nosocomial pathogens.

**Investigators:** Alwaleed Alaidan, Marie F. Bohol

### Project description

Strain typing is an invaluable tool for determining relatedness between isolates in a suspected outbreak. Each species of microorganisms has an almost limitless number of strains due to normal random mutations that occur in nature such as single base pair substitutions, deletion of individual genes, or even acquisition of DNA from other microbial species. Phenotypic characteristics such as bacterial biotyping, antibiograms, serotyping, and bacteriophage typing has been used to type strains. Unfortunately, these methods are limited by inconsistencies in their discriminating ability, their labor intensity, and their lack of reproducibility. Pulsed Field Gel Electrophoresis (PFGE) is a molecular subtyping method based on genotypic characteristics of an organism. It produces clearly interpretable results that are reproducible and have a highly discriminatory capability. It involves the separation of specific DNA fragments obtained from the whole DNA of an individual isolate by a unique electrophoresis technique capable of separating large DNA fragments, as well as small fragments. The DNA "fingerprint" produced can be compared to that of other isolates to determine their probable relatedness. For the current year number of isolates typed for Infection Control Unit in King Faisal Hospital & Research Centre increased comparing to the last year as shown below.

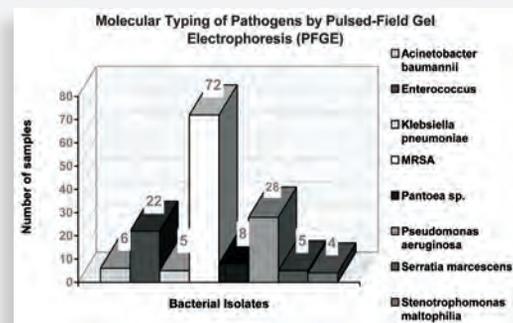
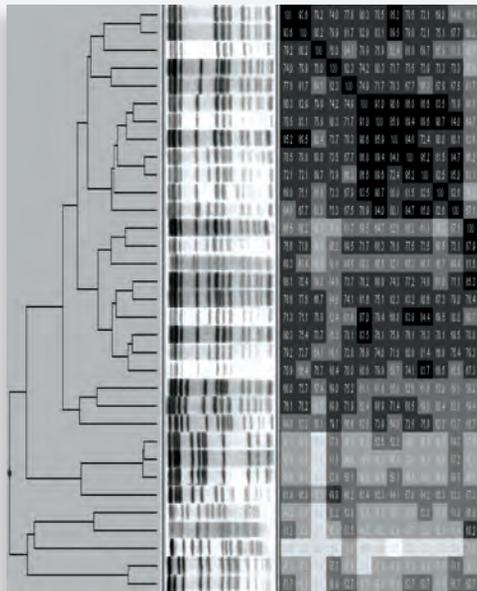


FIGURE 5. Bacterial isolates examined in this study.



**FIGURE 6.** Computer analysis of *Sma* I digested MRSA isolates, using BioNumerics software (Applied Maths).

**Progress**

To be continued.

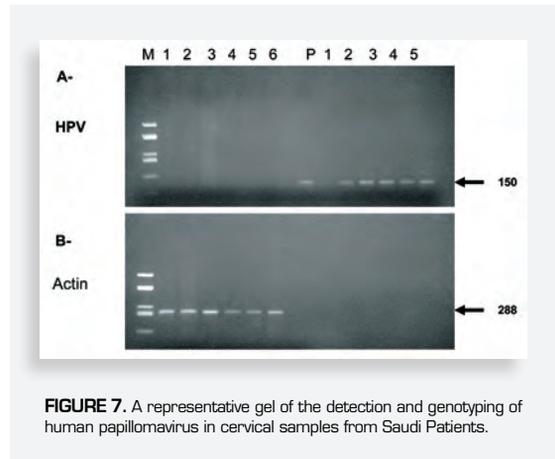
**Project title:** Detection and Genotyping of Human Papillomavirus in Cervical Samples from Saudi Patients. ORA Proposal # 2060038.

**Investigators:** Abdulrahman Al-suwaine, Alwaleed Alaidan

**Project description**

Cervical cancer is a major cause of death and it is the second most frequent type of cancer in women worldwide. Genital HPV is usually detected from patients'

clinical samples by PCR amplification methods. Two primer systems are commonly used; the MY09-MY11 primers and the GP5+GP6+ that amplify a wide range of HPV genotypes. Our initial results have shown that out of 62 cervical cancer samples tested using these primers, 51 (82%) samples were positive for the presence of Human Papillomavirus (Fig. 6).



**FIGURE 7.** A representative gel of the detection and genotyping of human papillomavirus in cervical samples from Saudi Patients.

**Progress**

To be completed.

**Project title:** Prevalence of Norovirus in Diarrheal Pediatric Patients.

**Investigators:** Hamsa Tayeb, Mohammed Al-Ahdal, Ahmed Al-Qahtani, and M. Carter

**Project description**

For the reason that the prevalence rates of rotavirus, enteric adenovirus and astrovirus are considered low as shown by our previous study, we decided to investigate the presence of other viruses causing infection before we can draw any conclusion. The norovirus group are small round structured viruses that cause diarrhea and have not been investigated before in Saudi Arabia. Distribution of norovirus was studied in 253 samples. Positivity was 2/46 (4.3%) in Jeddah, 5/81 (6.1%) in Makkah, and 2/126 (1.6%) in Riyadh. A total positivity of 9/253 (3.5%) was found. Results are shown in Table 2. For norovirus infection, no statistically significant difference between the number of infected children who are 1

year of age or less (44.4%) and those who are over 1 year of age (55.5%). Positivity ratio for male to female is all most equal, at 44.4% for male and 55.5% for female.

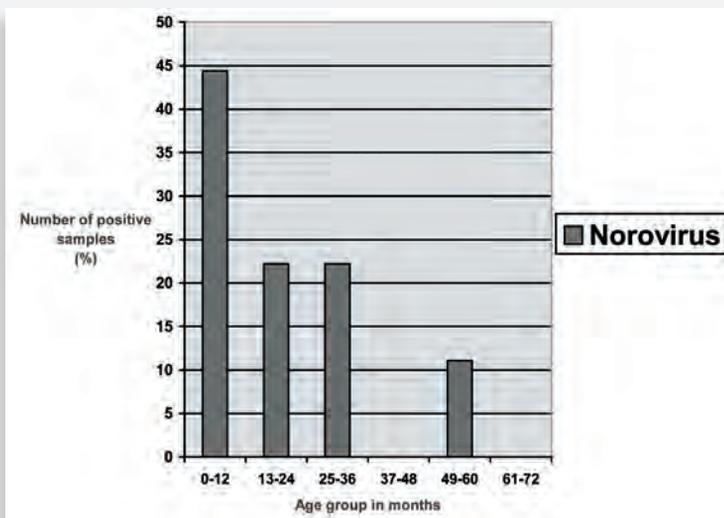
#### 15. Project title: Epstein Barr-Virus BART gene products.

Investigators: Maha A. Al-Mozaini, Mohammed N. Al-Ahdal, Paul J. Farrell

**TABLE 2.** Results of pediatric fecal samples screened for the presence of norovirus by ELISA.

City	Total Samples	Samples Tested	Norovirus Positive <sup>d</sup>	Positive [%]
Jeddah	205	46	2	4.3%
Makkah	405	81	5	6.1%
Riyadh	390	126	2	1.6%
Total	1000	253	9	3.5%

<sup>d</sup> Noroviruses were screened by an ELISA kit from Oxoid [IDEIATM, Cat# k6044]



**FIGURE 8.** Age distribution of ELISA-positive samples among children from three cities in Saudi Arabia (Jeddah, Makkah and Riyadh). The figure shows that the number of children infected with norovirus who are 1 year of age or less (44.4%) is near to those who are over 1 year of age (55.5%). No statistically significant difference was observed.

#### Project description

This project was carried out to produce recombinant RPMS1 and A73 proteins were it was expressed in *E. coli* and used to make monoclonal anti-RPMS1 and anti-A73 antibodies to role out their pathogenic roles which is still not understood. These monoclonal antibodies reacted specifically with artificially expressed RPMS1 and A73 but were not able to detect endogenous expression of A73 and RPMS1 proteins in a panel of EBV infected cell lines representing the different known types of EBV infection and in patient biopsies from EBV associated disease. This might still be a detection sensitivity problem because biochemical functions have been associated with the artificially expressed A73 and RPMS1 proteins. We also conducted computer analysis to compare the BART region of EBV with two other EBV strains (AG876 and GD1) and the related Rhesus and Callitricine lymphocryptovirus sequences, revealed conservation of the BART exon sequences and splice junctions. The similarity

and conservation support the validity of the deduced open reading frames and spliced structures.

#### Progress

Completed.



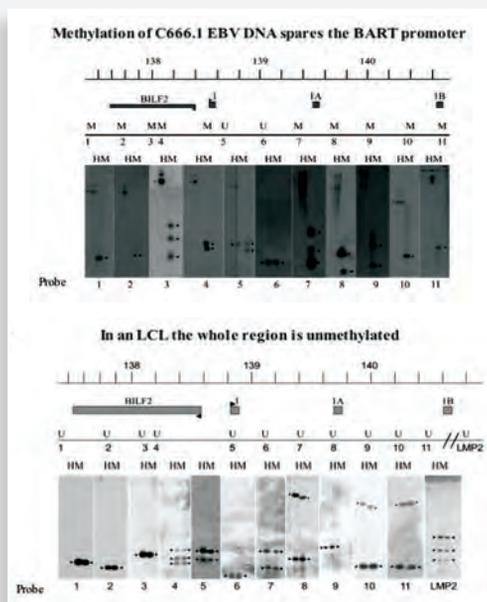
## Project description

Previous studies suggested that the promoter for the BART RNAs includes some downstream promoter elements located in the first intron. Most of the EBV genome is methylated in latently infected NPC cell lines but a 500bp region of unmethylated DNA was identified in the first intron of the EBV in C666.1 NPC cells using restriction enzyme digestion and bisulphite sequencing. This region may be protected from methylation by factors

bound to the DNA and correspond to part of the promoter for the BART RNAs since it was found to specifically bind proteins in nuclear extracts of the C666.1 cells in gel retardation assays. Sequence mapping of the binding regions suggested possible transcription factors that may regulate BART expression.

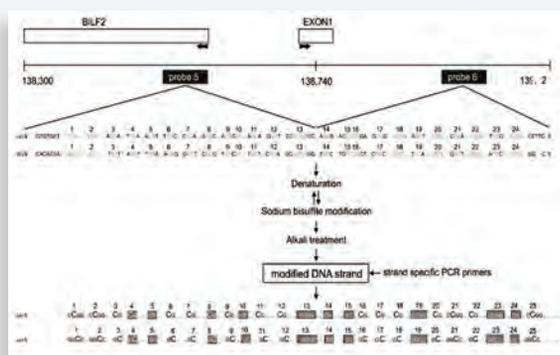
## Progress

Continuing.

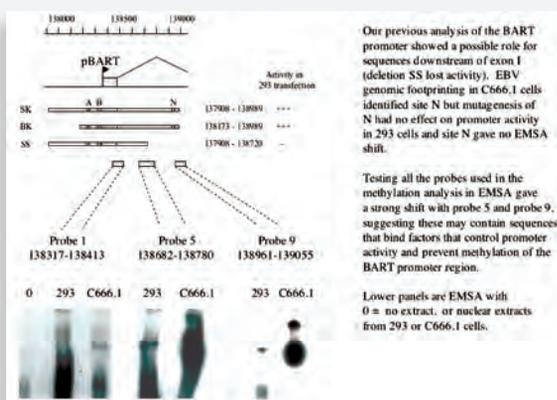


**Methylation of C666.1 and LCL EBV DNA near the pBART promoter.** DNA was digested with *HpaII* (H) or *MspI* (M) and analysed by Southern blotting using probes corresponding to the indicated regions 1-11. The positions of *HpaII* / *MspI* sites interpreted according to the EBV-wt sequence to be either unmethylated (U) or methylated (M) are indicated. The unmethylated region extends downstream of the BART transcription start.

The approximate locations of the probes are: 1 (137001-137320), 2 (137320-137640), 3 (137640-137930), 4 (137930-138180), 5 (138180-139750), 6 (138740-139050), 7 (139050-139380), 8 (139380-139750), 9 (139750-140090), 10 (140090-140430), and 11 (140430-140850). The predicted *MspI* fragments are marked with filled arrowheads. Methylated fragments resistant to *HpaII* are marked with filled circles.



**Methylation of individual CpG in C 666.1 cells near pBART promoter.** EBV-wt nucleotide, which are numbered 1-24. Probe 5 and 6, which showed unmethylated pattern by Southern blotting, contain 13 CpG in the probe 5 region and 11 CpG dinucleotides in the probe 6 region. Using bisulphite sequencing it was possible to distinguish the methylation status of each CpG dinucleotide. The capitalized bolded "C" shows the CpG dinucleotides that are methylated, whereas the CpG dinucleotide shown in a red box are those protected from methylation.



Our previous analysis of the BART promoter showed a possible role for sequences downstream of exon I (deletion SS lost activity). EBV genomic footprinting in C666.1 cells identified site N but mutagenesis of N had no effect on promoter activity in 293 cells and site N gave no EMSA shift.

Testing all the probes used in the methylation analysis in EMSA gave a strong shift with probe 5 and probe 9, suggesting these may contain sequences that bind factors that control promoter activity and prevent methylation of the BART promoter region.

Lower panels are EMSA with 0 = no extract, or nuclear extracts from 293 or C666.1 cells.

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### Submitted

- Alwaleed Alaidan, John Hays. 2007. Analysis of Tn1546 Elements within Vancomycin Resistant Enterococcus faecium. Submitted to the *Antimicrobial Agents and Chemotherapy*.

### Presentations

- Alwaleed Alaidan, Marie F. Bohol. Rapid pulsed-field gel electrophoresis (PFGE) protocol for typing *Serratia marcescens*. Presented at The 7<sup>th</sup> Annual Scientific Meeting of the International Epidemiology Association meeting. King Faisal Specialist Hospital and Research Centre (KFSH&RC), 27 to 29 November 2007.
- Maha Al-Mozaini. Epstein Barr-Virus BART Gene Products. Presented at Imperial college school of medicine, University of London UK. March 2007.
- Maha Al-Mozaini. Epstein Barr-Virus BART Gene Products. Presented at the 2nd Saudi Innovation Conference, Newcastle UK. 12 May 2007.
- Maha Al-Mozaini. Molecular Epidemiology of Transfusion Transmitted Virus among Saudis". Presented at The 7<sup>th</sup> Annual Scientific Meeting of the International Epidemiology Association meeting. King Faisal Specialist Hospital and Research Centre (KFSH&RC), 27 to 29 November 2007.

## Research Unit

# PROTEOMICS

The proteomics research unit aims to provide translational clinical cancer proteomics **(From Lab Bench to Bedside)**. More specifically, the unit examines the molecular alterations involved in different human solid epithelial tumors as well as hematological malignancies. State-of-the-art proteomics technologies are used for protein separation including high resolution 2-D gel electrophoresis (2-DE) and SELDI-protein Chip System. For automated protein identification of gel separated proteins MALDI-TOF mass spectrometry is utilized (figure1). Currently the complex protein expression patterns, decisive for the biological behavior and treatment sensitivity, of specific human solid tumors as well as hematological malignant and non malignant diseases are being examined.

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**Head:**

**Ayodele A. Alaiya, MB.BS, MPH, PhD**

**Members:**

Mai Al-Mohanna, PhD

Ibrahim Al-Duraibi, PhD

Maha Al-Eid, PhD

Zakia Shinwari MSc

Maha Al-Rodayan

**GOALS AND OBJECTIVES**

The goals of the proteomics research unit is to 1) Improve patient care through clinically relevant proteomics research. 2) Discover potential biomarkers for routine diagnostics and develop novel artificial tumor classifications using multivariate data analysis of differentially expressed proteins. 3) Encourage national and international collaborative proteomics projects and provide educational and training opportunities.

**PROGRESS**

The proteomics research unit has succeeded in establishing a functional clinical laboratory. Six research projects were approved by ORA within 2 years of commencement. Posters/published abstracts on three of the ongoing projects have been presented

at international meetings. Significant progress on the analysis of samples has been made. The unit has been awarded one KACST LGP Grant and another KACST ARP proposal has been submitted.

Two manuscripts are in preparation, pending protein identification work by mass spectrometry. A bench top MALDI-TOF MS instrument has been installed and it is anticipated that some of the data will be published this year.

Five in-house collaborative projects have been established this year with four research units at the Research Center and department of Neurosciences. We also have two international collaborative projects with Arabian Gulf University, Bahrain and Lund University, Sweden.

During the year, 6 trainees had basic training in proteomics in our unit.

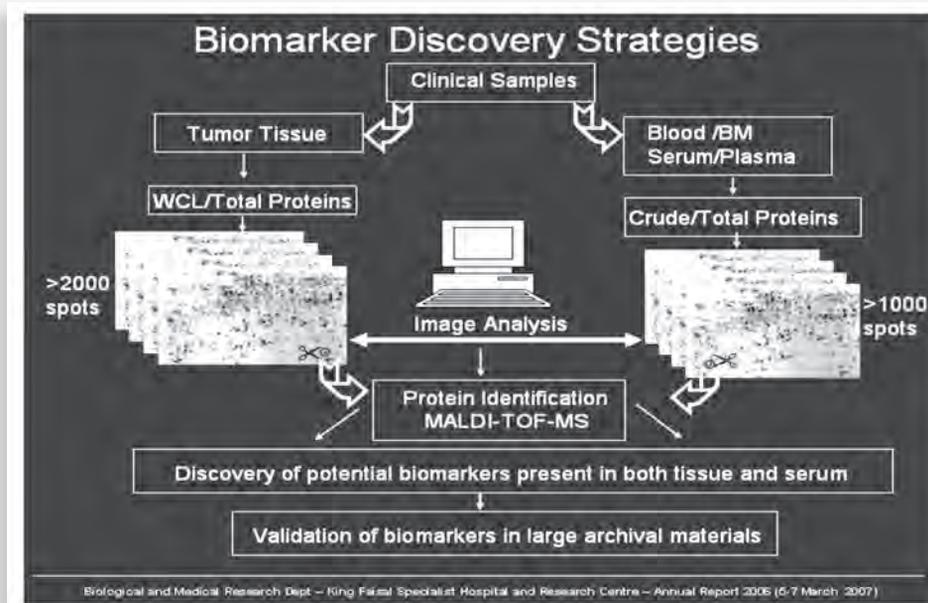


FIGURE 1

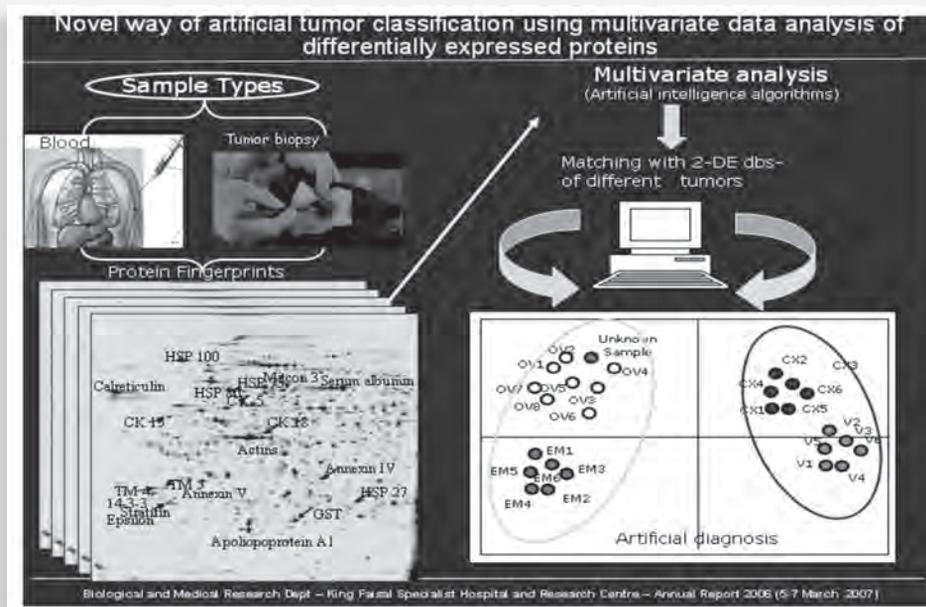


FIGURE 2

## RESEARCH PROJECTS

### OVERVIEW OF ON GOING PROJECTS

Title of Project	RAC #	Funding Agency	End of the project	Progress
1. Clinical proteomics: Development of Novel Biomarkers for Translational Ovarian Cancer Research	2050 011	KFSH&RC	December 2008	1st-year prog-ress report was approved by ORA
2. Protein profiling: Understanding the mechanisms of tumor response to therapy in a mouse model	2050 014	KFSH&RC	November 2008	Poster/abstract in 2006, Manuscript in preparation, Pending MALDI-TOF analysis
3. Clinical Cancer Proteomics: Understanding the cellular and molecular biology of prostate tumors	2050 026	KFSH&RC	December 2008	Manuscript in preparation, Pending MALDI-TOF analysis
4. Chronic myeloid leukemia: Development and validation of therapeutic hematoproteomics biomarkers	2050 040	KFSH&RC	April 2009	An abstract accepted at 6th HUPPO World Congress, Oct. 2007. Seoul, Korea
5. Clinical Proteomics: Development of novel biomarkers for diagnosis of Ovarian Cancer	2050 043	KACST LGP Grant	June 2008	Database of different types of pelvic mass is being constructed
6. Proteomics approach to biomarker discovery in Aplastic Anemia	2050 021	KFSH&RC	December 2009	An abstract accepted at 6th HUPPO World Congress, Oct. 2007. Seoul, Korea

### SUMMARY OF ON GOING PROJECTS

#### Proposal # 2050 040

Chronic Myeloid Leukemia: Development And Validation Of Therapeutic Hematoproteomic Biomarkers

**Running title: Protein Expression Profiling in Chronic Myeloid Leukemia**

**Principal Investigator:** Ayodele Abdulkareem Alaiya, MB.BS, MPH, PhD

**Co-Principal investigators:** Mahmoud Al-Jurf, MD & Naeem Chaudhri, MD

**Co-Investigators:** Mai Al-Mohanna, PhD, Entezam Sahovic, MD, Fahad Al Mohareb, MD, Fahad AL Sharif, MD, Hamad Al Omar, MD, Hazzaa Al Zahrani, MD, Ali

Al Shanqeeti, MD, Abdelghani Tbakhi, MD

#### Project description

This project focuses on the analysis of global protein expression profiles in patients with CML 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 help clinicians develop a customized treatment plan for individual patients.

### Progress

1. Sample processing/ optimization have been completed. Preliminary analysis has commenced. An abstract was accepted/published during 6th HUPO Annual World Congress held in Seoul, Korea Oct.2007.
2. Sample collection is on going (Nineteen samples have been collected so far)
3. Poster was presented during the above named congress.
4. Sample collection and treatment follow-up as well as post treatment sample collection is on going.

### Proposal # 2060 021

#### **Proteomics Approach To Biomarker Discovery In Aplastic Anemia**

**Principal Investigator:** Ayodele Abdulkareem Alaiya, MB.BS, MPH, PhD

**Co-Investigators:** Mahmoud Al-Jurf, MD, Naeem Chaudhri, MD, Mai Al-Mohanna, PhD, Entezam Sahovic, MD, Fahad Al Mohareb, MD, Fahad AL Sharif, MD, Hamad Al Omar, MD, Hazzaa Al Zahrani, MD, Ali Al Shanqeeti, MD and Abdelghani Tbakhi, MD

### Project description

This study focuses on the analysis of global protein expression profiles in patients with aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH) and hypoplastic myelodysplastic syndrome (MDS). 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 can differentially diagnose various bone marrow failure syndromes and provide accurate patient stratification. This will help clinicians reach an accurate diagnosis and consequently allow the development of an appropriate and rational therapeutic approach based on the individual patient's protein expression profile.

### Progress

1. Sample processing/ optimization have been completed. Preliminary analysis has commenced. A combined abstract on preliminary data using

FFE analysis of Aplastic anemia and CML samples was accepted during 6th HUPO Annual World Congress held in Seoul, Korea Oct.2007.

2. Sample collection has been ongoing since Nov 2006. (Only 7 samples have been collected so far due to the low incidence (1-3 per million) of the disease).
3. Sample collection is on going.

### Proposal # 2050 043

#### **Clinical Proteomics: Development Of Novel Biomarkers For Diagnosis Of Ovarian Cancer**

Funded by King Abdulaziz City for Science & Technology (KACST) under the Limited Grants Program.

**Principal Investigator:** Ayodele Abdulkareem Alaiya, MB.BS, MPH, PhD

**Co-Investigators:** Mai Al-Mohanna, PhD, Hany Al-Salem, MD, Ismail Al- Badawi, MD, Jamal Al-Subhi, MD, Nada Al- Sahan, MD and Asma Tulba MD

This project focuses on the analysis of global protein expression profiles in patients diagnosed with sporadic common epithelial ovarian tumor. Both normal and tumor tissue as well as serum samples will be analyzed from the same patients using 2D gel electrophoresis and computer assisted image analysis.

The goal of our work is to develop tools for the accurate classification of borderline tumors. With this purpose in mind, mini-2-DE gels will be utilized for the proteome analysis. This technology is 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. KACST Funding was made available in June 2007.
2. Preliminary analysis of samples is ongoing. A database of different types of pelvic mass' is being generated.
3. Sample collection is ongoing (Twenty samples have been collected so far)

**Proposal # 2050 014****Protein profiling: Understanding The Mechanisms Of Tumor Response To Therapy In A Mouse Model**

**Principal Investigator:** Ayodele Abdulkareem Alaiya, MB.BS, MPH, PhD

**Co-Investigators:** Mai Al-Mohanna, PhD, Raafat El-Sayed, DVM & Falah Al-Mohanna, DVM

**Project description**

This pilot study is based on a mouse 4T1 breast tumor model. The 4T1 mammary carcinoma cell line is transplantable and the tumor grows 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. These characteristics of 4T1 make it suitable for an in vivo experimental animal model of human breast 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. First-year progress report has been approved by ORA. This is a prospective study involving fresh clinical tissue specimens. New cases are being added and the analysis is on going.
2. An abstract was accepted during 5th HUPPO world congress at Long Beach California, 28th Oct -1st Nov 2006.
3. A poster was presented during the above mentioned meeting
4. A manuscript is in preparation
5. Analysis of serum samples has started and protein identification work is pending optimization of the newly installed MALDI-TOF-MS instrument.

**Proposal # 2050 011****Clinical proteomics: Development of Novel Biomarkers for Translational Ovarian Cancer Research**

**Principal Investigator:** Ayodele Abdulkareem Alaiya, MB.BS, MPH, PhD

**Co-Investigators:** Mai Al-Mohanna, PhD, Adnan

Munkarah, MD, Hany Al-Salem, MD, Ismail Al-Badawi, MD, Jamal Al-Subhi, MD, Nada Al-Sahan, MD, Asma Tulba MD & Nayer Cheema, MD.

**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.

Normal and tumor tissue as well as serum samples will be analyzed from the same patients using 2D 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 capable of predicting whether a patient's response to therapy will be total, incomplete or negligible. This information will help clinicians to choose the appropriate treatment for individual patients.

**Progress**

First-year progress report has been approved by ORA. This is a prospective study involving fresh clinical tissue specimens. Over 50 samples have been collected and 24 cases have met the inclusion criteria and have been analyzed. We are awaiting clinical and pathological reports to allow us to select interesting protein spots for identification by mass spectrometry analysis. A draft manuscript is currently in preparation.

**Proposal # 2050 026****Clinical Cancer Proteomics: Understanding The Cellular And Molecular Biology Of Prostate Tumors**

**Principal Investigator:** Ayodele Abdulkareem Alaiya, MB.BS, MPH, PhD

**Co-Principal Investigator:** Ali Bin Mahfooz, MD

**Co-Investigators:** Mai Al-Mohanna, PhD, Mohammad Aslam, MD, Irfan Ahmed, MD, and Kamal Hanash, MD

**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 use, and commence a wider scan of the prostate proteome for carcinoma specific markers. Novel proteins will be characterized by means of highly sensitive mass spectrometry and if necessary sequence analysis.

### Progress

1. First-year progress report has been approved by ORA. Since this is a prospective study involving fresh clinical tissue specimens, new cases are being added and the analysis is ongoing.
2. Of the thirty three (33) samples collected only 25 have met the inclusion criteria.
3. Awaiting clinical/pathological data for selecting potential protein spot for identification by mass spectrometry
4. Preliminary data is planned for presentation during the Urology Department Clinical Grand Rounds.

### FUTURE RESEARCH DIRECTION

Recent progress in the proteomics field has commenced the search for markers that define different diseases, including malignant transformation, malignancy potential and tumor treatment sensitivity. These markers will be of the utmost importance for early cancer detection and the development of individualized therapy.

A number of potential biomarkers have been identified by proteome studies. Our goal is to validate some of the potential biomarkers in different disease conditions using other methods such as immunohistochemistry. The importance of this is to convince clinicians that these markers have prognostic or treatment predictive value in consecutive patient's materials.

Proteome data generated will also be translated into artificial learning models; which can be used for diagnosis, prognosis and treatment prediction.

Our preliminary data indicates that analysis of proteome data has an enormous potential to further develop into a "proteome scanner", i.e., an artificial intelligence tool capable of assisting clinical decisions in establishing more accurate diagnosis and prognosis (Figure 2).

### PUBLICATIONS

#### Most recent International scientific meetings with accepted abstracts/Poster Presentations

- Application of Free Flow Electrophoresis (FFE) for proteomic analysis of plasma, serum and bone marrow of Chronic Myeloid Leukemia and Aplastic Anemia patients, Mai Al Mohanna, Mahmoud Al Jurf, Mikkel Nissum, Maha Al Eid, Fahad Al Mohareb, Naeem Chaudhri, Fahad Al Sharif, Randa Al Nounou, Tarek Owaidah and, Ayodele Alaiya HUPO, 6<sup>th</sup> World Annual Congress, Proteomics: From technology development to Biomarker Applications, October 6-10, 2007, COEX Seoul, Korea. (Poster), abstract published in *Cellular and Molecular Proteomics Journal*.
- Chronic Myeloid Leukemia Global Opinion Leader Summit (CML GOLs), in Athens, Greece on 2 – 4 March 2007.
- Proteomic Profiling of an Experimental Baboon Model of Heatstroke, Ayodele A. Alaiya, Mai Al-Mohanna, Mohammed Dehbi, Maha Al-Eid, Aaron Kwaasi, George Roberts & Abderrezak Bouchama, Joint 3<sup>rd</sup> AOHUPO & 4<sup>th</sup> Structural Biology and Functional Genomics Conference 4-7 Dec 2006, Singapore (Poster Presentation).
- Differential Protein Expression Changes During Tumor Response to Therapy Ayodele A. Alaiya, Mai Almohanna, Maha Al-Eid, Falah Al-Mohanna, Muhammad Azhar Chishti, Raafat El-Sayed and Stig Linder. HUPO 5th Annual World Congress Translating Proteomics from Bench to Bedside, Long Beach, California, USA, 28<sup>th</sup> Oct – 1<sup>st</sup> Nov. 2006 (Poster Presentation).
- Characterization Of The Expression Of HTm4 (MS4A3), A Cell Cycle Regulator, In Human Peripheral Blood Cells And Normal Malignant Tissues Jeffery L. Kutok, Xing Yang, Ayodele Alaiya, Rebecca Folkerth and Chaker Adra. Joint 3<sup>rd</sup> AOHUPO & 4<sup>th</sup> Structural Biology and Functional Genomics Conference 4-7 Dec 2006, Singapore (Poster Presentation).
- Mobilization Of Autologous Hematopoietic Stem Cells By Targeting The CXCR4-SDF-1a Axis Is Associated With Prolongation Of Islet Allograft Survival. Fiorina Paolo, Jurewicz Mollie, Vergani Andrea, Gebhard Thoma, Zerwes Hans-Guenter, Sayegh Mohamed, Abdi Reza , Ayodele Alaiya and Chaker Adra. Joint 3<sup>rd</sup> AOHUPO & 4<sup>th</sup> Structural Biology and Functional Genomics Conference 4-7 Dec 2006, Singapore (Poster Presentation).

### Recently Published Scientific Papers

- Sofia Bengtsson, Morten Krogh, Cristina Al-Khalili Szigyarto, Mathias Uhlen, Kjell Schedvins, Claes Silfverswärd, Stig Linder, Gert Auer, Ayodele Alaiya, and Peter James Large-Scale Proteomics Analysis of Human Ovarian Cancer for Biomarkers. *J. Proteome Res.*; 2007; 6(4) pp 1440 – 1450.  
[http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17315909&ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17315909&ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum)
- Liu Z, Bengtsson S, Krogh M, Marquez M, Nilsson S, James P, Alaiya A, Holmberg AR, Somatostatin effects on the proteome of the LNCaP cell-line. *Int J Oncol.* 2007 May;30(5):1173-9  
<http://www.ncbi.nlm.nih.gov/sites/entrez>
- Ayodele Alaiya and Stig Linder, Clinical Cancer proteomics, in Proteomics & Peptidomics – Technology Developments Driving Biology, Chapter 16, COAC-vol-46:Edited by György Marko-Varga (Elsevier Science, 2005).
- Ayodele Alaiya, Mai Al-Mohanna and Stig Linder: Clinical Cancer Proteomics: Promises and Pitfalls, *Journal of Proteome Research* 2005, 4, 1213- 1222 1213.
- Carlen, L.M., Sanchez, F., Bergman, A.C., Becker, S., Hirschberg, D., Franzen, B., Coffey, J., Jornvall, H., Auer, G., Alaiya, A.A. & Stahle, M. (2005). Proteome analysis of skin distinguishes acute guttate from chronic plaque psoriasis. *Journal of Investigative Dermatology*, 124, 63-9.
- Liu Z, Marquez M, Nilsson S, Holmberg AR and Alaiya AA: Proteomic analysis of a human prostate cancer cell line after incubation with a novel somatostatin-14 derivative. *Cancer Genomics & Proteomics* 2: 347-352, 2005.

# **BIOMEDICAL PHYSICS**



## The Department of

# BIOMEDICAL PHYSICS

The Biomedical Physics Department is a very composite department which covers a diversity of functions. Its mission is to provide service, research, consultation and education within and outside KFSH&RC through its Radiation Physics, Imaging Physics, Health Physics/Radiation Safety, Biomedical Physics Research, Radiation Safety, Gamma Irradiation and Secondary Standard Dosimetry components.

The department devotes a large part of its efforts to clinical service. Our staff assist in the planning of treatment for patient undergoing radiation therapy and are also responsible for the proper calibration and function of radiation equipment. We also provides physics support services to other hospital-based operations for diagnostic procedures and for the safe and effective use of all forms of radiation as well as for maintaining a high quality radiation safety program at KFSH&RC. Our research program focuses on how to provide fundamental information as how to make best use of radiation for the therapy of cancer. There have been number of presentations and papers accepted and published, submitted and in preparation from the approved research projects in Biomedical Physics, details of which are highlighted in the sectional reports.

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### *Chairman*

**Belal Moftah, PhD, MCCPM**

### *Deputy Chairman*

Ghazi Alsbeih, MD, PhD

### *Administrative Staff*

Josephine Veridiano, BSc

Irene Banguilan, BSc (RC Grant)

The Gamma Irradiation Facility has continued to provide sterilization services for KFSH&RC departments, and for outside institutions. The Secondary Standard Dosimetry Laboratory remains a major service with increasing activity in the calibration of survey meters and other radiation equipment. It is our objective for these services to develop into valuable income producing assets.

Teaching is also a major function of the department. Our staff had participated in a number of training and education programs through lectures to Radiology residents, university students, KFSH&RC employees and other professionals from collaborating institutions. The continuing education among the staff members is maintained through attendance at international and local meetings. The Journal Club Presentation meeting is ongoing where all staff members are given the chance to present. The Department is preparing for a residency training program in medical physics and pursuing the initiative of getting its staff members board certified, by internationally recognized certifying bodies in medical physics.

The activities of the following sections and core facilities which constitute the Department are shown in separate reports:

BIOMEDICAL PHYSICS DEPARTMENT	
SECTIONS	CORE FACILITIES
Radiation Physics	Gamma Irradiation
Imaging Physics	Secondary Standard Dosimetry Laboratory
Health Physics	
Biomedical Physics Research	
Radiation Safety Office	

## RESEARCH PROJECTS

Many research projects have been started and producing results. Details of these projects are found in the sectional reports.

## FUTURE RESEARCH DIRECTION

We look forward to participate in interdisciplinary research with the clinical care departments with emphasis on the new technologies which are coming on line. Future research will be conducted and focused toward improving quality patient care for cancer patients. The future research direction for all sections and core facilities of the Biomedical Physics Department is also highlighted in the sectional reports.

## PUBLICATIONS

The Department has published a number of papers, from approved research projects, in international journals. Details of 2007 publications are listed in each section/core facility report.

## Research Unit

# RADIATION BIOLOGY LABORATORY

*B*ioomedical physics provides the physical and biological basis for the many uses of radiation in medicine and allied health profession. Radiation biology is the biological arm that is devoted to study the effect of radiations on living organisms. The objective is to understand and master this tool in health and medicine in order to harness its beneficial effects and avoid its hazardous potential.

The research laboratory continued its close collaboration with the Oncology Department. Radiation therapy is a major arm of cancer treatment and management. Radiation doses prescribed should provide maximum tumor control while keeping normal tissues' complications very low. This could be achieved by better separating between the curves of tumor control probability (TCP) and normal tissue complication probability (NTCP) using predictive assays for radiosensitivity (Figure 1). The radiosensitivity of tumors and normal tissues varies considerably between patients. The objective of the current research work is to improve therapeutic ratio of radiotherapy by improving NTCP. Therefore, research focuses on studying the genetic determinants of radiosensitivity in Saudi cancer patients.

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### *Head*

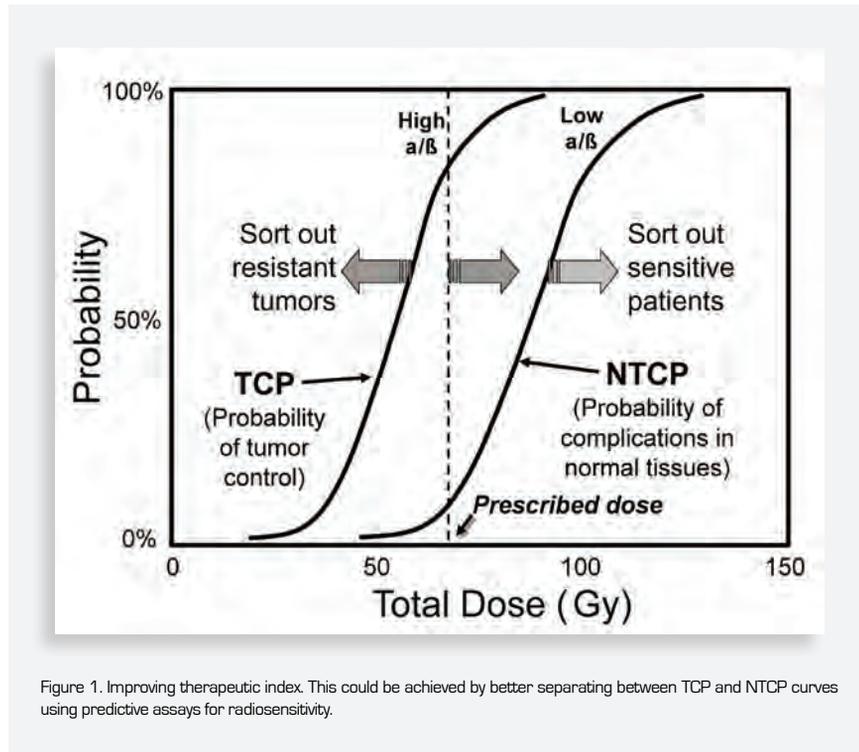
**Ghazi Alsbeih, PhD**

### *Members*

Najla Al-Harbi, BSc

Muneera Al-Buhairi, BSc

Khaled Al-Hadyan, BSc (Grant)



## RESEARCH PROJECTS

**Project title: Study Comparing Radiosensitivity, DNA Repair, Misrepair And Alterations In Protein Expression Between Fibroblasts Derived From Patients Having Different Normal Tissue Reactions To Radiotherapy: Potential For A Predictive Assay (RAC# 2000 031)**

**Investigators:** G. Alsbeih, N. Al-Rajhi, A. Alaam, M. Al-Sebaie, Najla Al-Harbi and Muneera Al-Buhairi

### Project description

Most cancer patients (50-70%) receive radiation treatment during the management of their disease. Recent advances in imaging and optimization of radiation delivery and tumor targeting will improve patient outcome and allow for dose escalation. However, the tolerance of normal tissues constitutes the limiting factor for dose escalation in radiotherapy. Patients vary considerably

in their normal tissue response to radiotherapy even after similar treatment. The causes of this variability are not well understood but have been linked to cellular radiosensitivity, which is largely attributed to putative genetic factors. The aim of this project is to identify these factors that influence and control radiosensitivity. The endpoints include clonogenic survival, DNA repair, proteins and genes expression, cell aging and senescence, and polymorphic genetic variations that have been more recently investigated as cause of differences between patients.

### Progress

The requirements to individualize radiotherapy treatment of Saudi cancer patients are:

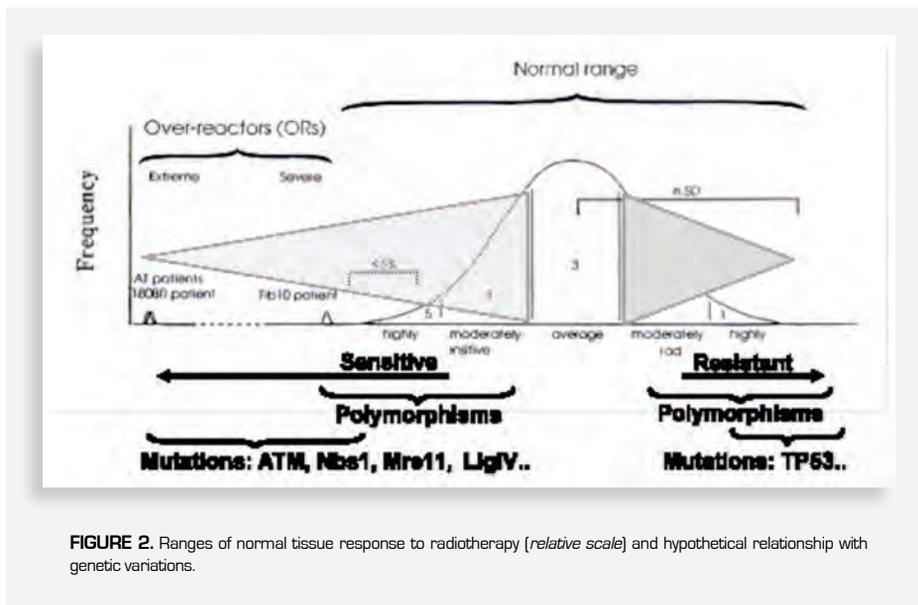
1. Existence of variations in radiosensitivity between patients
2. Existence of a relationship between radiation complications and radiosensitivity
3. Molecular determinants of RS to identify markers

to use in clinic as prognostic or predictive factors. We studied:

- \* Protein expression: working blocks in the cells
- \* Genetic variations Single Nucleotide Polymorphisms (SNPs): that can affect transcription, translation, or amino acid sequence of protein

We have previously studied requirement 1 and 2 that were confirmed. We also showed a correlation between p53 or p21 proteins (encoded by TP53 and CDKN1A genes, respectively) induction following irradiation and inherent radiation sensitivity. To shed light on the genetic factors involved, we hypothesized that amino acid substitution variants in these two highly radiation responsive proteins are associated with, and could explain individual variations in radiosensitivity (Figure 2).

normal controls). The genotype distribution in function of radiosensitivity is illustrated in figure 4. Significant association was observed between SF2 and ATM 1853 Asn, XRCC3 241 Met and TGFβ1 10 Leu alleles ( $P = 0.05$ ,  $0.02$  and  $0.02$ , respectively). The number of risk alleles increased with increasing radiosensitivity and groups' comparison showed statistically significant difference between the radiosensitive and the control groups ( $P \leq 0.001$ ). We conclude that SNPs in susceptible genes influence cellular radiation response and that the number of risk alleles has combined effect on radiosensitivity. Individuals with multiple risk alleles could be more susceptible to radiation effects than those with less risk alleles. These results may have implications in predicting normal tissue reactions to radiotherapy and risk assessment of radiation exposure.



**FIGURE 2.** Ranges of normal tissue response to radiotherapy (*relative scale*) and hypothetical relationship with genetic variations.

We set out to identify genetic predictive markers of radiosensitivity. The study included 4 amino acid substitution variants in candidate genes (ATM 1853 Asp/Asn G>A, XRCC1 399 Arg/Gln G>A, XRCC3 241 Thr/Met C>T and TGFβ1 10 Leu/Pro T>C). These were genotyped by direct sequencing in 54 fibroblast strains of different radiosensitivity (26 radiosensitive cases and 28

## FUTURE RESEARCH DIRECTION

We currently carry out the study on Head and Neck cancer patients treated with radiotherapy. We looking for the association between the presence of certain genetic variations and late reactions to radiotherapy,

## PUBLICATIONS

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### Manuscripts

- G. Alsbeih, N. Al-Harbi, M. Al-Buhairi, K. Al-Hadyan and M. Al-Hamed. Association between TP53 Codon72 Single Nucleotide Polymorphism and Radiation Sensitivity of Human Fibroblasts. *Radiation Research*. 167(5), 535-540, 2007.  
This paper was podcasted by the Radiation Research Journal. The podcast containing the interview with the author went live with the publication of the manuscript in May 2007 at the website: <http://lsmr1.lbl.gov:8080/xwiki/bin/view/Radiation+Research+Society/>.
- Alsbeih G, El-Sebaie M, Al-Harbi N, Al-Buhairi M, Al-Hadyan K, Al-Rajhi N. Radiosensitivity of Human Fibroblasts is Associated with Amino Acid Substitution Variants in Susceptible Genes and Correlates with the Number of Risk Alleles. *International Journal of Radiation Oncology, Biology and Physics*. 68(1), 229-235, 2007.
- G. Alsbeih, M. Torres, N. Al-Harbi, and M. Al-Buhairi. Evidence that Individual Variations in TP53 and CDKN1A Protein Responsiveness are Related to Inherent Radiation Sensitivity. *Radiation Research*, 167, 58-65, 2007.

### Abstracts/Congress Proceedings

- Al-Hadyan K., Al-Harbi N., and Alsbeih G. Assessment

of the Frequency of a Novel MRE11 Mutation Responsible of the Rare Ataxia Telangiectasia-Like Disorder in Saudi Population. 2<sup>nd</sup> Pan Arab Human Genetics Conference, Dubai 20-22 November 2007.

- Ghazi Alsbeih, Najla Al-Harbi, Medhat El-Sebaie, Nasser Al-Rajhi, Muneera Al-Buhairi, Khaled Al-Hadyan and Khaled Abu-Amro. Association Between XRCC1 G339A Polymorphism and Radiation-induced Fibrosis in Nasopharyngeal Cancer Patients. 1<sup>st</sup> Conference on Normal Tissue Radiation Effects (CONTRE), Las Vegas, Nevada, USA, 12-41 July 2007.
- R. Kodym, G. Alsbeih, M. Story. Multiple molecular Alterations in Fibroblasts of a Patient with radiation Hypersensitivity / Chromosomal Fragility Syndrome. 13<sup>th</sup> International Congress of Radiation Research (ICRR), San Francisco, California, USA, 8-12 July 2007.

Ghazi Alsbeih, Najla Al-Harbi, Khaled Al-Hadyan, Muneera Al-Buhairi, Medhat El-Sebaie, Nasser Al-Rajhi. Association Between Polymorphisms in Candidate Genes and Late Complications to Radiotherapy in Head and Neck Cancer Patients. 13<sup>th</sup> International Congress of Radiation Research (ICRR) & San Francisco Radiation Oncology Conference (SFROC), San Francisco, California, USA, 8-12 July 2007. \*Winner of an ICRR Award 2007. Scientific news press communication in Saudi local newspapers addressed to general public.

## Research Unit

# CLINICAL DOSIMETRY AND TREATMENT PLANNING

In 2007 there was a nine-fold increase of patients being planned using IMRT (Intensity Modulated Radiation Therapy). IMRT provides better dose coverage for tumors and minimization of dose to critical organs and normal tissue. In addition to these advantages, for patients with nasopharyngeal tumor, the parotids are spared thereby preventing xerostomia. This technique involves a heavy investment of human resources due to the complexity of planning and extensive QA for each and every patient.

CT planning for breast was introduced using field in field method for missing tissue compensation. CT planning for the breast using CT images provides better dose uniformity.

For the year 2008, IMRT will continue to be employed for increasing number of patients due to the advantages mentioned above. In addition, IGRT (Image Guided Radiation Therapy) would be introduced to further improve the accuracy of treatment.

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### *Head*

**Michael Lim, CMD, ACT**

### *Members*

Ghadeer Nazer, BSc

Hind Al-Selham, BSc (on study leave)

Huda Al-Mohammed, BSc, CMD (on study leave)

Manal Owedha, BSc

Paula Yates, CMD

Sarah Ashmeg, BSc

Wedyan Safer, BSc

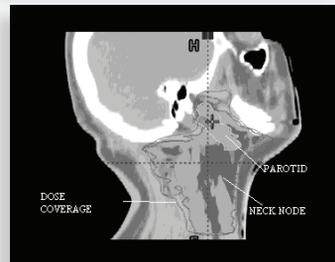
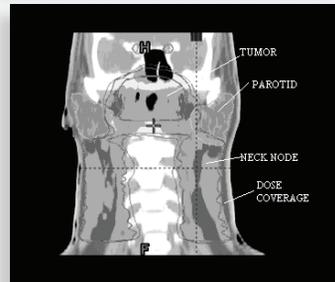
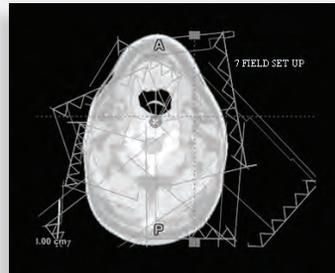
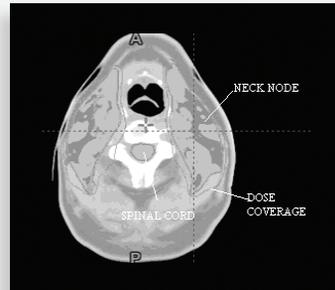
**CORE SERVICE ACTIVITIES**

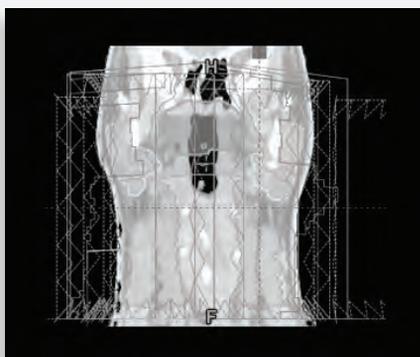
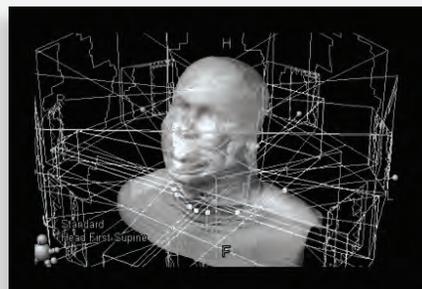
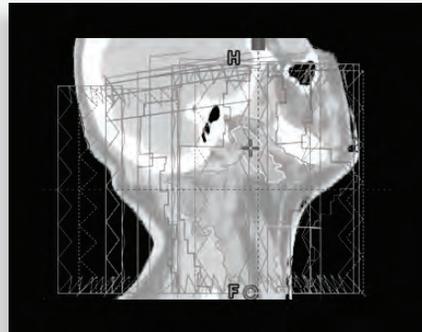
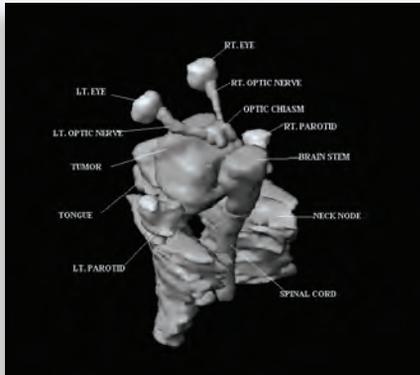
ACTIVITIES	YEAR 2007
MU Calculation	799
TBI Calculation	54
TDF Calculation	20
3D CT Treatment Planning	1222
2D Contour Treatment Planning	235
Stereotactic Radiosurgery/ Radiotherapy	9
Electron Cutout Measurement	218
TLD Dosimetry	54
HDR Brachytherapy	13
LDR Brachytherapy	15
IMRT	27
Compensator Fabrication and Measurement	2
Clinical Consultation	48
QA	48
<b>TOTAL PROCEDURES</b>	<b>2764</b>
<b>PATIENTS</b>	<b>1570</b>
<b>MANHOURS</b>	<b>8181</b>

**TRAINING AND EDUCATION ACTIVITIES**

We continue to provide training in clinical dosimetry and treatment planning to physics graduates from different universities within the Kingdom. In collaboration with the International Atomic Energy Agency (IAEA), a five-day dosimetry and treatment planning workshop shall be conducted at King Faisal Specialist Hospital & Research Centre in April 2008.

**IMRT FOR NASOPHARYNGEAL CANCER**







## Core Facility

# GAMMA IRRADIATION FACILITY

*T*he 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 industries; and (3) to provide a high activity radioactive source for variety of research projects.

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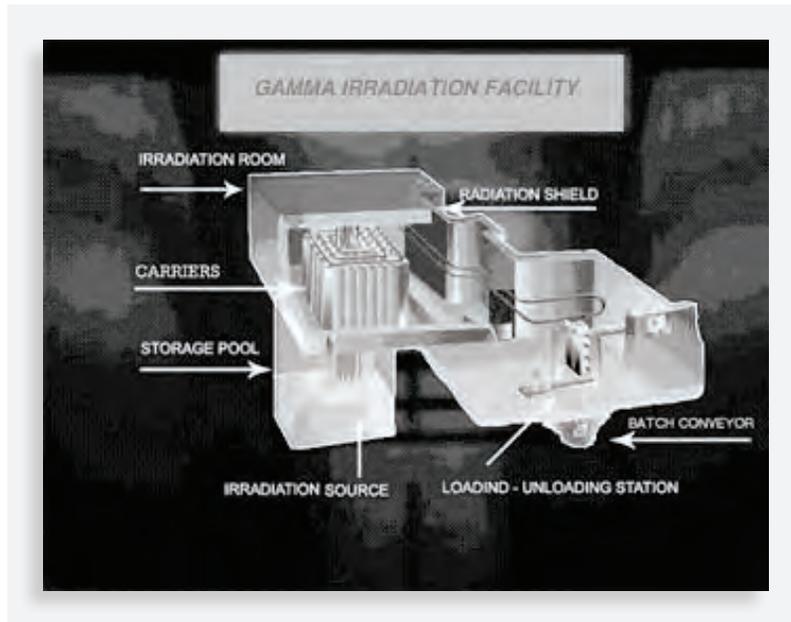
### *Head*

**Akram Al-Moussa, BSc**

### *Members*

Saad Bin-Jamaan, BSc

Edilberto delos Reyes

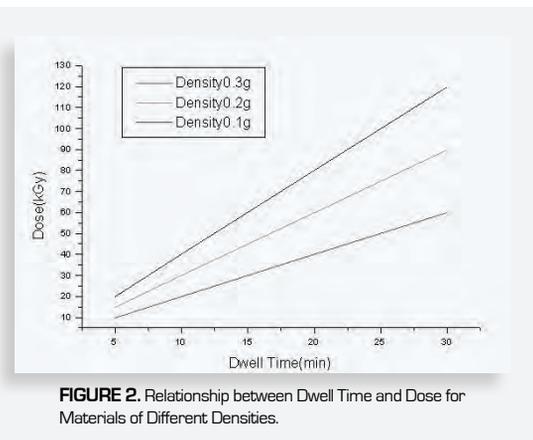


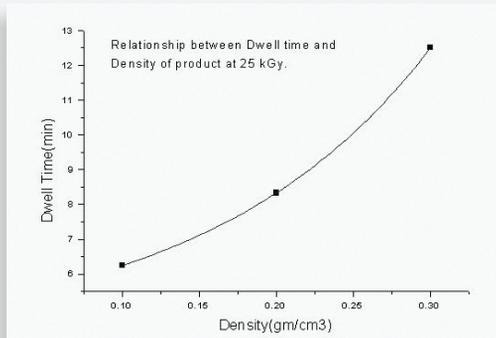
## CORE SERVICE ACTIVITIES

The activities of the Gamma Irradiation Facility in 2007 are as follows:

1. Continued to provide sterilization for hospital needs (Cyclotron kits and supplies of ART laboratory).
2. Provided gamma irradiation services for One Master Degree student from King Saud University, College of Pharmaceutical Science, and another student from College of Agriculture and food science joined him for his graduation project on food preservation. (More than 150 hrs of irradiation of their samples was done with doing the necessary dosimetry for all these samples.)
3. Conducted inter-comparison study with RISO National Laboratory, DENMARK which is one of two best standard laboratories (the second after NPL). Resulting in very accurate dosimetry, less than 1% (0.66%) difference between our dose and their measurement.
4. ISO auditing done successfully without any major comment

5. Research project with KACST on the film dosimetry are going, trying to modify a new high dose dosimeter.
6. New proposed strategy for running GIF was investigated taken in consideration applications that can only be sterilized in GIF.





**FIGURE 3.** Relationship between Dwell Time (time of irradiation) and Density of Irradiated Materials.

## GAMMA RAY STERILIZATION

The Gamma Irradiation Facility has continued to provide sterilization services for the different departments of KFSH&RC and other institutions on a fee for service basis. Sterilization of different items such as pharmaceuticals for Tabuk Company and Riyadh Pharma and some frequent customers, such as National Guard Hospital. About SR16,000 was the income of GIF last year. The Facility will pursue its income generating opportunities through sterilization of medical products/materials using gamma irradiation.



## Research Unit

# HEALTH PHYSICS

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 obtained the King Abdulaziz City for Science & Technology (KACST) as the only reference laboratory for personnel radiation dose monitoring and instrument calibration and therefore the number of clientele increased by about 20-25% from last year. It obtained recognition from the International Atomic Energy Agency (IAEA) as the center for developing experts on radiation protection in interventional radiology with the continuing technical support for the research project on radiation protection. The Research Centre was made the recipient of equipment and supplies for the research project on radiation safety in Interventional Radiology. One abstract on radiation doses in pediatric cardiac catheterization was selected and was the only manuscript from Saudi Arabia to be presented in the European Commission Conference. The Section takes pride in the establishment of technical and research collaboration with Italy and member countries of the European Commission on radiation protection in interventional radiology.

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### *Head*

**Abdalla N. Al-Haj, PhD CSRP**  
**Kostas Chantziantoniu, MSc DABR**

### *Members*

Amal Al-Mutairi, BSc (RC Grant)  
 Celestino S. Lagarde, BSc  
 Charle Lagarde, MSc  
 Heba Al-Humaidan, BSc  
 Ibrahim Al-Gain, BSc  
 Nabil I'Gilan, MSc  
 Rana Al-Qwiz (RC Grant)

## HEALTH PHYSICS ACTIVITIES

The table below summarizes the accomplishments made by the Health Physics Section for year 2007 in providing services to the KFSH&RC institution, to other facilities in the Kingdom of Saudi Arabia and surrounding countries in the Gulf region [Fig. 1].

Task	Quantity
Radiation workers monitored for occupational doses	15,987
Patients surveyed for radiation level	282
Patients rooms surveyed for radiation level	282
Patients rooms decontaminated	276
Equipment surveyed for contamination	36
TLD badges irradiated for quality control of TLD readers of outside facilities	180
Consultative advice provided	9
Training courses & educational lectures provided	37

## RESEARCH PROJECTS

**Project title: Development of a National Core of Expertise in Radiation Safety for Patients Protection in Interventional Practices (in collaboration with the Radiation Safety Office and with the technical assistance from IAEA)**

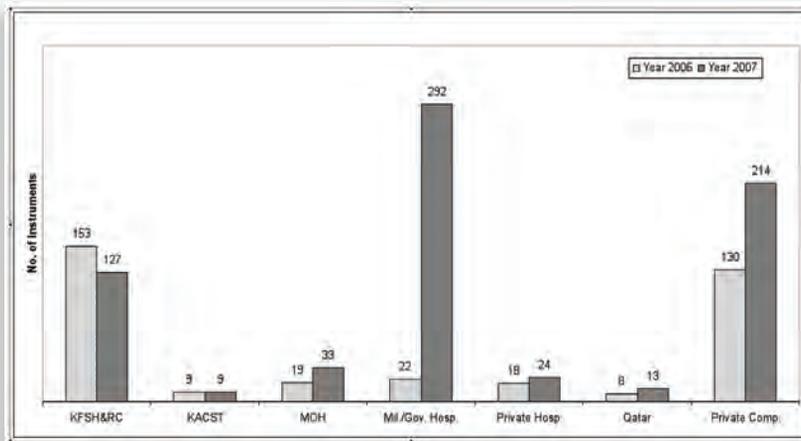
**Investigator:** Abdalla N. Al-Haj, PhD

### Project description

The project assesses the radiation doses to patients and investigates the parameters that contribute to these doses. The project aims to identify procedures that give high patient doses and risks so that dose reduction techniques could be further studied.

### Progress

The IAEA technical assistance has been completed but the research project is still continuing to include other hospitals.



**FIGURE 1.** Graph showing the number of instruments and institutions that are being served for instrument calibration in year 2007.

## FUTURE RESEARCH DIRECTION

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New research endeavors are being planned to be undertaken on radiation dose assessment in computed tomography (CT) procedures.

## PUBLICATIONS

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### Abstracts accepted for presentation

- A. Al-Haj. "Variation in Radiation Doses in Pediatric Cardiac Catheterization: Basis for Optimizing Radiation Protection", abstract approved for oral presentation and publication in the proceedings of the Safety & Efficacy for New Techniques and Imaging Using New Equipment to Support European Legislation held on 18-20 April 2007, Delft, The Netherlands
- A. Al-Haj. "Preliminary Results of the IAEA\_KFSHRC Coordinated Research Project on Radiation Safety for Patient Protection in Interventional Radiology Practices" abstract approved for oral presentation in the 2nd Saudi International Medical Physics Conference held on 7-8 May 2007.

- A. Lobriguito. Calibration of Radiochromic "Films for Patient Dosimetry in Interventional Radiology" abstract approved for oral presentation in the 2nd Saudi International Medical Physics Conference held on 7-8 May 2007.

### Manuscripts approved for publication

- A. A. Alghamdi, J. Al-Mokhleif, A. Al-Haj, N. M. Spyrou "Feasibility Study of using PET to Determine Nitrogen Concentration after High Energy Photon Irradiation", Journal of Radioanalytical and Nuclear Chemistry, Vol. 271, No. 3, 783 – 789,(2007).
- A. Al-Haj, C Lagarde, F. Mahyoub. "A Comparative Study on the Susceptibility of LiF:Mg: Ti (TLD-100) and LiF:Mg:Cu:P (TLD-100H) to Spurious Signals in Thermoluminescence Dosimetry" Radiation Protection Dosimetry, 125: 399-402 (2007).



## Research Unit

# IMAGING PHYSICS

Most of the activities in the imaging physics section are concentrated in 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. The imaging modalities assisted are: dentistry, 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).

Many of the clinical services provided fall under the broad category of imaging equipment implementation: starting 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. The 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 dose calibrators, evaluate and implement new imaging technology, assist in clinical trials, and perform 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 physics and nuclear medicine physics.

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### *Head*

**Kostas Chantzantoniou, MSc DABR**

### *Members*

Adnan Z. Al-Watban, PhD

Nabil I'Qilan, MSc

Omer Demirkaya, PhD

Refaat Y. Al-Mazrou, MSc

Sarah Ashmeg, BSc (RC Grant Employee)

## 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 as whole-body images exhibit 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. 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 Standard Uptake Values (SUV) from a lesion volume. It may also allow them to track small changes in lesion characteristics, which may be difficult to observe visually.



#### 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.

### Project title: Brain Injury in Heatstroke: Study Using Diffusion MRI, MR-Spectroscopy and PET in Experimental Baboon

**Investigators:** A. Bouchama, M. Al-Gahtani, Z. Patay, A. Al-Sugair, O. Demirkaya, F. Al-Mohanna, R. El-Sayed and M. Dehbi

#### Project description

This study, in general, aims at 1) testing the hypothesis that neuralgic injury of heat stroke is due to cerebral ischemia, 2) identifying susceptible brain regions to ischemia, and 3) investigating whether cellular energy metabolism, cell membranes, and neuronal integrity and inflammation are associated with heatstroke related brain damage. Our contribution will be studying some of these affects quantitatively using PET dynamic imaging protocols in conjunction with kinetic modeling.

#### Progress

KACST grant received and project will commence.

### Project title: Computational and Experimental Analysis of 3 Untranslated Regions and Poly A Signal to Site Distance Requirements: Use in Translationally Active Linear DNA

**Investigators:** O. Demirkaya and K. Abu-Khabar

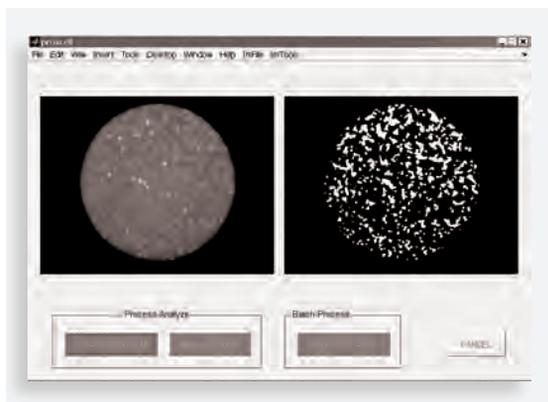
#### Project description

In this project, we have been developing automated methods for quantification of the levels of the protein expression in live cells as evaluated by fluorescence of green fluorescent protein cells using image processing and analysis techniques.

#### Progress

We have developed, in MATLAB environment, a fully automated approach that quantifies/analyzes the estimate of protein expression (see the figure below). We have built a stand-alone graphical user interface (GUI) (see the screenshot of the GUI above) that allows the user to process images in batch or single mode. A manuscript in which data was analyzed using this method

has been accepted for publication. We are working on the images acquired by a new 96-well setup. It requires some changes in the image segmentation procedures.



**Project title: Performance Test Data Analysis of Scintillation Cameras**

**Investigators:** O. Demirkaya and R. Al Mazrou

**Project description**

Acceptance and quality control (QC) testing of gamma cameras are essential to both measuring the performance characteristics and ensuring that images produced by the gamma camera system are clinically acceptable. There are a battery of tests performed routinely on gamma cameras to verify their stability and performance. Among these, uniformity and resolution tests are probably the most frequently performed. Normally, more extensive testing is performed at installation to check if the camera meets the performance specifications claimed by the manufacturer. Calculation of the performance parameters can be quite sophisticated and not be done manually. The aim of this project was to develop methods to calculate the performance parameters of gamma cameras from the test data conducted according to the (National Electrical Manufacturers Association) (NEMA) guidelines.

**Progress**

We have developed a set of image analysis tools to calculate the performance parameters of scintillation cameras and SPECT systems from test data acquired according to the NEMA NU 1-2001 guidelines. The calculation methods are either completely automated or require minimal user interaction; minimizing potential



human errors. The developed methods are robust with respect to varying conditions under which these tests may be performed. The core algorithms have been validated for accuracy. They have been extensively tested on images acquired by the gamma cameras from different vendors. All the algorithms are incorporated into a graphical user interface that provides a convenient way to process the data and report the results. The entire application has been developed in MATLAB programming environment and is compiled to run as a stand-alone program. The developed image analysis tools provide an automated, convenient and accurate means to calculate the performance parameters of gamma cameras and SPECT systems. The application has also proved to be a very useful tool in our workshops and trainings. A manuscript describing the methods has been published. The ongoing research is trying to use this tool for trending

**FUTURE RESEARCH DIRECTION**

The primary activity of the clinical research being performed 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, many of which are pediatric. It is also our intention to establish a functional and molecular imaging research lab to conduct basic as well as clinical research projects.

## PUBLICATIONS

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### Abstracts accepted for presentation

- Omer Demirkaya and Refaat Al Mazrou. A Software Application to Calculate the Performance Parameters of Gamma Cameras, accepted for InfoSNM oral presentation, NM 54<sup>th</sup> Annual Meeting, Washington, DC, June 2-6, 2007.
- Omer Demirkaya, Mohei Abouzied, and Ayman Rifai. Quantification of Bone Metastasis in whole body images of 18F-FDG PET/CT, accepted for oral presentation, NM 54<sup>th</sup> Annual Meeting, Washington, DC, June 2-6, 2007.
- Kostas Chantziantoniou. Development of MATLAB Application to Measure and Map Patient Entrance Doses in Cardiac Cath Lab Procedures Using GafChromic XR Type R film as a Dosimetry Media, 2<sup>nd</sup> International Saudi Symposium on Medical Physics: Update and Advances, Riyadh Military Hospital, Riyadh, Saudi Arabia. May 2007.
- Refaat Al-Mazrou and Omer Demirkaya. Testing of Five Gamma Camera Systems Using NEMA NU1-2001 Guidelines, 2<sup>nd</sup> International Saudi Symposium on Medical Physics: Update and Advances, Riyadh Military Hospital, Riyadh, Saudi Arabia. May 2007.

### Manuscripts approved for publication

- Omer Demirkaya and Refaat Al Mazrou. Performance Test Data Analysis of Gamma Cameras, *IEEE Transaction on Nuclear Science*, 5:1506-1515, 2007.

## Research Unit

# RADIATION PHYSICS

The primary activities of the Radiation Physics Section have been devoted to providing clinical physics and quality assurance services to cancer patients receiving radiation therapy treatments. The section's responsibilities include: quality control on therapeutic linear accelerators, simulator, treatment planning systems and brachytherapy equipment. The section also plays a vital role in selecting suitable radiation therapy equipment, designing shielded facilities and obtaining accurate data collection from equipment for clinical services. The Clinical Dosimetry and Treatment Planning Unit of this section, provides all planning and clinical dosimetry services for radiation therapy patients.

Our Section supports the treatment of 1570 cancer patients, providing 2764 medical physics procedures for the year.

The Radiation Physics Section, in collaboration with the King Faisal Cancer Center, has launched the state-of-the-art Intensity Modulated Radiation Therapy (IMRT) technique. Following the successful launching of the state-of-the-art IMRT technique, the section head has closely the radiation physicists to increase the number of patients treated with IMRT making IMRT a routine cancer treatment technique at KFSH&RC. Now we have treated more than 100 IMRT patients, covering more than 24 tumor sites. This advanced mode of high-precision radiotherapy treatment is a major accomplishment for RC, KFCC, KFSH&RC and the Kingdom.

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### *Head*

**Belal Moftah, Ph.D., MCCPM**

### *Members*

Mohd Abdullah Al-Kafi, MSc

Huda Al-Mohammed, BSc, CMD (On study leave)

Jazi Al-Mokhef, MS, ABR (until March 2007)

Waleed Al-Najjar, PhD, ABR

Raju Francis Alookkaran, MSc

Hind Al-Selham, BSc (on study leave)

Eman Al-Sulaimani, MSc

Sarah Ashmeg, BSc (RC Grant)

Manal Awidh, BSc

Tarek El-Kaissi, PhD

Michael Lim, CMD, ACT

Fareed Mahyoub, MSc

Paula Michelle Yates, CMD

Ghadeer Nazer, BSc

Ahmed Nobah, MSc

Wedyan Safer, BSc

Priority for next year is the development and implementation of innovative radiotherapy techniques such as IGRT and IORT as well as engineering of affiliation contracts with major radiotherapy vendors to turn our Radiation Therapy service into a reference site for Saudi and Middle East customers.

Our Section's aim is to help turn our services into a centre of excellence in clinical medical physics and radiation oncology.

## RESEARCH PROJECTS

**Project title: Establishment of a Monte Carlo-based Clinical Dosimetry Center in Saudi Arabia. (Project # 2060 026)**

**Principal Investigator:** Belal Moftah

### 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, the following tasks have been accomplished by the investigators team at KFSH&RC: Movement of the project from Jeddah to KFSH&RC-Riyadh; Purchase of three dual processor computers to set up a proto-type Monte-Carlo computer cluster; EGSnrcMP Monte Carlo system code was installed and commissioned on the dual processor computers, "commissioned" three clinical beams at KFSH&RC; Percent Depth Dose (PDD) and beam profiles for 6, 10 and 18 MV photons that are used clinically at KFSH&RC were calculated and compared with the clinical measurements with a very good agreements; An abstract for these preliminary clinical results has been delivered at the 16th International Conference on Medical Physics, Dubai, April 14-16, 2008; Performed systems search and review for Monte Carlo computer cluster system for the project. (KACST Project No. AT-25-85 - Approved funding: SR 652,000)

## FUTURE CLINICAL RESEARCH DIRECTION

**Project title: Image-Guided Radiation Therapy (IGRT) and Adaptive Gated Radiotherapy**

### Project description

IGRT is considered the world's most advanced radiotherapy technique for the treatment of cancer patients. It is an automated patient positioning system that pinpoints internal tumors, corrects patient set-up and tracks patient movement throughout treatment. Adaptive Gating detects the exact location of a moving target in real-time, enabling respiration-triggered dose delivery. The project's aim is to provide these modalities to our cancer patients undergoing radiotherapy treatment.

### Progress

Research in preparation. As part of this year radiotherapy tender, we are going to receive three IGRT systems from World leading providers of IGRT to provide our cancer patients with the best-diversified treatment options. With these selections, KFSH&RC will be the first site in the world to offer state-of-the-art radiotherapy techniques combining all of these three cutting-edge machines. KFSH&RC will be the first center to provide IGRT technique outside Europe and North America. A research proposal will be drafted and submitted.

**Project title: Incorporation of PET/CT 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. This project is to investigate the usefulness of hardware co-registered PET/CT images for target volume definition for three dimensional conformal radiation therapy treatment planning.

### Progress

Research in preparatory stage. Multi-disciplinary research group from different KFSH&RC departments has been formed. Software was acquired and treatment planning procedure was written. A research project will be submitted.

## PUBLICATIONS

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### Publications in Peer-Reviewed Journals

- Slobodan Devic, Tê Vuong, Belal Moftah, Michael Evans, Ervin B. Podgorsak, Emily Poon and Frank Verhaegen, Image Guided High Dose Rate Endorectal Brachytherapy, *Medical Physics* 34 (2007) 4451-4458.
- David F. Measday, Trevor J. Stocki, Belal A. Moftah, and Heywood Tam, Rays from Muon Capture in  $^{27}\text{Al}$  and Natural Si, *Physical Review C* 76 035504 (2007).

### Conference Proceedings and Abstracts

- Belal Moftah (Speaker and Organizer), IMRT Show-and-Tell Workshop, "Radiation Oncology Emerging Technology Symposium", KFSH&RC, Riyadh, May 29-30, 2007.
- Abdel Ghani, Nabeel Maalej, Michael Lim, Tarek El-Kaissi, Belal Moftah, IMRT Patient Dose Verification Using Radiochromic Film, 2-D Array, and Electronic Portal Imaging Device (EPID), 2<sup>nd</sup> International Saudi Symposium on Medical Physics, Riyadh Military Hospital, May 7-9, 2007.
- Tarek El-Kaissi, Ahmad Nobah, Fareed Mayhoub, Belal Moftah, MOSFET Dose Measurement for Total Body Irradiation (TBI) Patients, 2<sup>nd</sup> International Saudi Symposium on Medical Physics, Riyadh Military Hospital, May 7-9, 2007.
- Belal Moftah, IMRT in Head and Neck Radiotherapy, Third Annual Conference of the Radiological Society of Saudi Arabia (RSSA 3), Jeddah, April 9-12, 2007.
- Belal Moftah, Intensity Modulated Radiotherapy (IMRT), "Oncology Update 2007 Symposium: Expanding Horizons", King Faisal Specialist Hospital and Research Centre, Intercontinental Hotel, Jeddah, Saudi Arabia, Feb 28, 2007.

### Presentations at Scientific meetings

(Presenting author denoted by\*)

- Belal Moftah\*, Intensity Modulated Radiotherapy (IMRT) Experience at KFSH&RC, Intensity Modulated Radiation Therapy Launching Ceremony, KFSH&RC, Riyadh, June 12, 2007.
- Belal Moftah\*, IMRT Process & Experience at KFSH, "Radiation Oncology Emerging Technology Symposium", Marriott Hotel, Riyadh, May 29, 2007.
- Belal Moftah\*, IMRT in Head and Neck Radiotherapy, Third Annual Conference of the Radiological Society of Saudi Arabia (RSSA 3), Jeddah, April 9-12, 2007.
- Belal Moftah\*, Intensity Modulated Radiotherapy (IMRT), "Oncology Update 2007 Symposium: Expanding Horizons", King Faisal Specialist Hospital and Research Centre, Intercontinental Hotel, Jeddah, Saudi Arabia, Feb 28, 2007.
- Ganiyu Adeniyi Asuni\*, Nabil Maalej, Belal Moftah, IMRT Patient Dose Verification Using Radiochromic Film, 2-D Array, and Electronic Portal Imaging Device (EPID). 2<sup>nd</sup> International Saudi Symposium on Medical Physics, Riyadh, May 7-9 2007.
- Saleh A. Al-Ashrah\*, Nabil Maalej, Esam Eldeen Rahmatalla, Hasan Al-Gamdi, Belal Moftah, Radiochromic Film Measurement and Monte Carlo Calculation of Surface Dose from 6 MV Beam. 2<sup>nd</sup> International Saudi Symposium on Medical Physics, Riyadh, May 7-9 2007.
- Abdullah Al-Amro\*, Adnan Al-Hebshi, Medhat El-Sebaie, Karen Leigh Long, Michael Lim, Tarek El-Kaissi, Belal Moftah, Stereotactic Radiosurgery/Radiation Therapy: King Faisal Cancer Center Experience, "Symposium on Advanced Precision Radiotherapy", 2<sup>nd</sup> BrainLAB European RT User Meeting, Rome, Italy, May 3-6, 2007.



## Research Unit

# RADIATION SAFETY OFFICE

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

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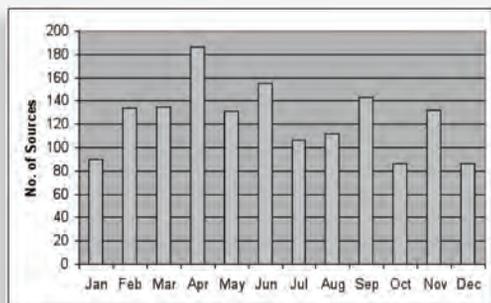
### *Head*

**Fareed H. Mahyoub, MSc**

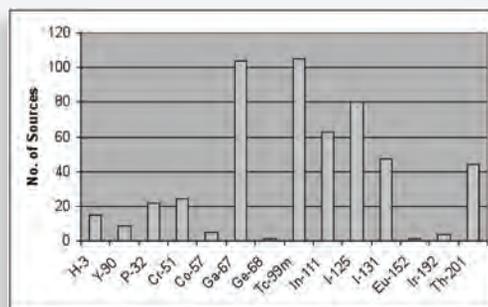
### *Members*

Ibrahim K. Al-Anazi, MSc

Celestino Lagarde, BS (Shared)



**FIGURE 1.** Graph showing the monthly out-going packages for year 2007.



**FIGURE 2.** Graph showing the number of imported sources of radioactive isotopes in year 2007.

## RSO ACTIVITIES

For the year 2007, the RSO applied for amendment and renewal of the KFSH&RC license from KACST for the radiation facilities of Nuclear Medicine and radiation therapy and the applications have been successfully approved. It has renewed the KACST license to import radioactive materials and has submitted the application for the renewal of a license for the Gamma Irradiation facility. Three certifications were issued for importation of radioactive materials. In radiation measurements, there were 454 incoming sources and 1496 out-going packages of radioactive materials surveyed. In the principle of "As Low as Reasonably Achievable" (ALARA), 84 investigations were carried out on staff whose occupational doses exceeded the ALARA levels; 21 thyroid bioassays were performed. Five work areas and 2 equipments were surveyed for radiation and contamination levels. A total of 30 radioactive sealed sources were checked for inventory and 15 leak tests were undertaken. The RSO responded to 3 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 78 drums were surveyed and stored in Warehouse No. 6 and 46 drums of wastes were disposed. In education and training the RSO conducted

3 in-house lectures and provided a two-week on-the-job training on radiation safety to 5 university students. 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-NEW RADIOACTIVE WASTE BUILDING

The construction phase of the new Radioactive Waste Building was finished in 2007. The RSO was given the lead role in preparation for its operation. The RSO has supervised the final phase before operation and assured that the building has met the national requirements and standards by communicating with regulatory bodies such as KACST, Ministry of Interior, and the Civil Defense. The interlock system and the security alarm and access system were all evaluated to ensure compliance with national regulatory requirements for radiation protection during emergencies. The RSO also, has successfully transferred all radioactive waste in a safely manner from Warehouse-6 to the new facility without any incidents. All licensing requirements were submitted to KACST and the new facility was fully operated in December 2007.

## Core Facility

# SECONDARY STANDARD DOSIMETRY LABORATORY

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 and to other institutions in the Kingdom of Saudi Arabia and the Gulf region.

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### *Head*

**Jazi Al-Mokhlef, MSc DABR**

### *Members*

Abdalla AH-Haj, PhD  
Aida Lobriquito, MSc  
Celestino Lagarde, BSc  
Heba AH-Humaidan, BSc  
Nabil IQilan, MSc  
Rana Al-Qwiz, BSc

**ACTIVITIES**

For the year 2007, the SSDL provided calibration services to 5 Departments of KFSH&RC, 4 government agencies, 6 government hospitals, 8 private hospitals, 42 private companies and extended the provision of calibration services to 1 country in the Gulf region as well [Fig 1]. A total of 712 radiation-measuring instruments were calibrated, inter-compared and acceptance tested. These instruments include 489 survey meters, 215

pocket dosimeters, 4 radiotherapy dosimeters and 4 diagnostic dosimeters [Fig. 2]. A total of 38 quality control tests of counting systems were performed. It has also provided irradiation services for the quality control test of thermoluminescent dosimeter (TLD) readers of service providers in the Kingdom where a total of 180 TLD badges were irradiated. 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.

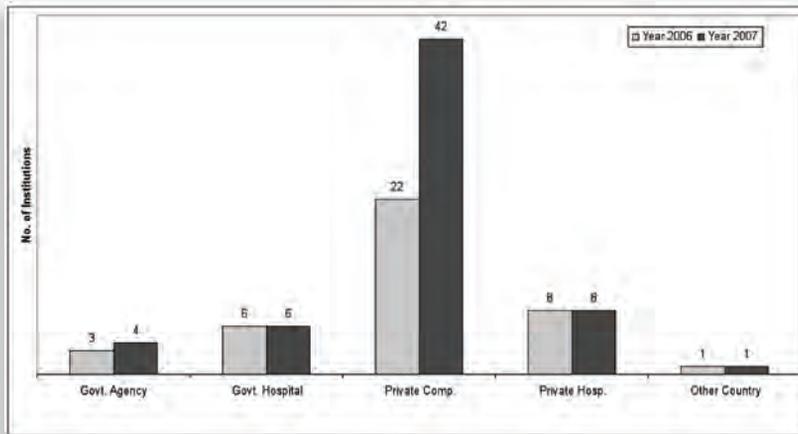


FIGURE 1. Graph showing the number of external facilities served by the SSDL in year 2007.

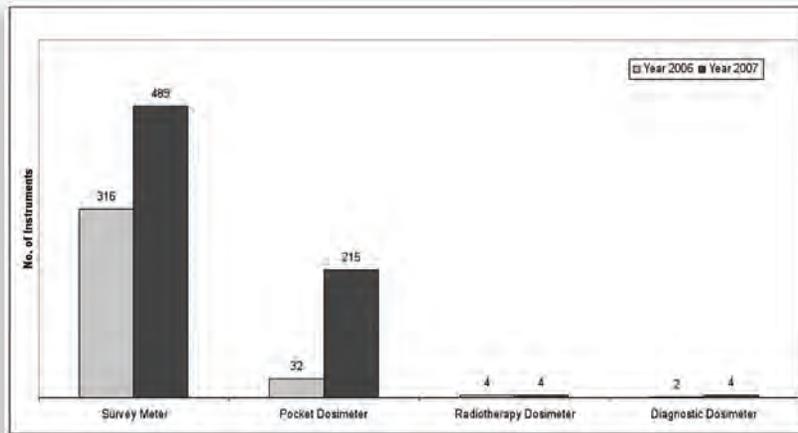


FIGURE 2. Graph showing the type and number of instruments calibrated in year 2007.

**BIostatistics EPIDEMIOLOGY AND  
SCIENTIFIC COMPUTING**



## The Department of

# BIostatistics EPIdemiology AND SCIENTIFIC COMPUTING

The year 2007 has been a year of accomplishments for the Department of Biostatistics and Epidemiology. The most significant contributions are the tremendous effort made by the Epidemiology Research Unit to host the 7<sup>th</sup> International Epidemiology Association in November 2007, and the associated workshops. The expansion of several Web-based registries to multi-centers, and serious planning to become regional. Moreover the collaboration with the Liver Transplant Department helped in the establishment of the Ban Arab Liver Transplant Registry. The Technical Data Base Core Facility has proven to be the “State-of-the-art Information Technology provider” for our Institution. The Computing Services Core Facility continues to provide users support on many technical issues. Its member are simply indispensable. It is clear to the Department that its role is recognized by higher administration as important to the Institution’s pursuit of its overall mission - the provision of core quantitative support in the areas of biostatistics and epidemiology, the research into epidemiological issues that affect the health of patients and the population of the Kingdom at large, and the development of new methodologies into the analysis of biomedical data.

Organizationally, the Department is structured into six groups - biostatistics, epidemiology, computing services, registries, technical databases and administrative

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### *Chairman*

**Mohamed Shoukri, PhD**

### *Administrative Support Staff*

Cielo Dupaya-Mendiola

Ismail El Sayed S. Mohammed

Mailah Pamela Moreto

Abel Pangilinan



## Research Unit

# BIOSTATISTICS

The Biostatistics Research Unit (BRU) enjoys a special status in the Department. We are motivated by the curiosity of clinicians and scientists to pursue knowledge for its own sake and for what it may yield. Knowledge - whether newly discovered or interpreted by our researchers or newly acquired, is a powerful agent of change in the lives of our staff and the hospital community in general. The most interesting feature of the BRU is its ability to transform itself to serve the Hospital and Research Centre well and effectively. Our commitment to fulfill the mission of the Research Centre and the Hospital is distilled in our Mission:

The BRU of the BESC, is dedicated to the advancement of scientific research through the development of statistical methodologies and their applications in biomedical research. The BRU staff shall be engaged in critical thinking, in developing and sustaining their practical skills. By pursuing these objectives, the BRU endeavors to serve the RC, the Hospital, and the interests of the society.

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**Head:****Gamal El Din Hassan Mohamed, PhD****Members:**

Dilek Colak  
Naser Elkum  
Pranesh Kumar  
Mohamed Shoukri  
Salah Al-Gain  
Abdelmuneim Eldali  
Samia Al-Hashim  
Wilhelmina Ventura

## RESEARCH PROJECTS

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**Project title: Establishing Equivalence of Two Treatments using Neyman's C ( $\alpha$ ) Test (RAC # 2050002)**

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

### Project description

The determination of bio-equivalence 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 " testing procedure. It possesses an interesting property in that it is locally most powerful against alternatives in the neighborhood of the null.

### Progress

The 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 test. Monte Carlo simulations have been conducted to achieve this objective.

**Project title: The Power of Detecting Heterogeneity in Meta-Analysis (RAC# 2060032)**

**Investigators:** M.M. Shoukri and G. El-Din Mohamed

### Project description

Meta analysis (MA) may be defined as the quantitative review and synthesis of the results of related but independent studies. The objectives of MA can of several-fold. First, combining the information over different studies, an integrated analysis will have statistical power to detect treatment effect than an analysis based on only one study. Second, when several studies have conflicting conclusions, an MA can be used to estimate an average treatment effect, called effect size (ES) or to identify a subset of studies associated with a beneficial effect. This objective is achieved by identifying the degree of heterogeneity among the studies. Thirdly, summarizing the uncertainty within and between studies will help us to establish a more realistic approach to hypothesis testing and confidence interval construction.

A good illustrative example of this is the data from 41 randomized trials of a new surgical treatment of stomach ulcer that were considered by Efron (1996). In this study the ES that is of interest is the log-odds ratio (LODR). The LODR estimates from this study showed a substantial heterogeneity in the estimated effects among the studies. Higgins and Thompson (2002) indicated that one of the most crucial and difficult aspect in many systematic reviews is addressing the statistical heterogeneity. Besides quantifying the heterogeneity, it is helpful o understand the causes of heterogeneity among studies.

A random effect is typically used to account for heterogeneity in MA, and thus heterogeneity variance is an important parameter under this model. In practice a simple and commonly used estimator for heterogeneity variance is the method of moment's estimator proposed by DerSimonian and Laird (DL) (1986). Another estimator of variance heterogeneity was recently proposed by Sidik and Jonkman (2005) (SJ), which can be applied regardless of the effect size. Therefore the total variance of the effect is the sum of two components, the first being the between studies variance and the other is the within study variance.

This proposal deals with the problem of between and within studies heterogeneity. Although the within study heterogeneity is always reported with each study,

one can reduce its level by employing an appropriate transformation. The issue of reducing the within study heterogeneity and proper estimation of the between studies variance and their joint effect on the power of detecting heterogeneity will be explored in this proposal.

### Study Objectives

This proposal has several objectives:

1. Instead of using the LODR is an effect size, we shall use the Risk Difference (RD). The reason being, there is only one traditionally transformation to normality when the odds ratio is used as an effect size. Therefore, we have no other competing transformation. However, if the RD is used, several competing alternatives exist to stabilize the variance of the RD: the logit, the inverse sign, and the Wald are examples of such transformations.
2. The chi square distribution has been used to test for heterogeneity in MA, by approximating the test of homogeneity  $Q$  using its first two moments (see Jackson 2006). We propose an alternative model other than the chi square approximation. The proposed approximation should account for the possible skewness in the reported effect sizes, and is expected to improve the power of the test. To be specific, instead of using a two-moment approximation, we propose the three parameters Johnson's family of distribution (1970).
3. It is noted that most MA studies focus on the randomized controlled clinical trials (RCCT). However, there are situations when the number of RCCT may not be sufficient, and one would be tempted to mix RCCT with other studies. This mixture is likely to increase the heterogeneity. However, through meta-regression one should be able to account for differences in these study designs and increase the power of detecting significant over all effect size.
4. The proposed methodology will be illustrated on studies that investigate the effect of Folic Acid taken by pregnant women on Neural tube defects among new born.

### Progress

Data from 12 randomized controlled double blind studies that attempted to correlate use of folic acid to neural tube defects have been collected and analyzed. The reviewed studies used the odds ratio as an effect

measure. The over all odds ratio (combined odds ratio under fixed effects model) was not significant, indicating lack of association between folic acid intake and neural tube defects among new borns. Fortunately, the raw data were available and it was possible for us to re-analyze each study and conduct meta analysis, using the risk difference as an effect measure. To our surprise, the results were substantially different. This indicates that the final results of a meta analysis depends in some way on the type of effect measure being used. We therefore planned a power analysis and improve on the chi-square approximation test of heterogeneity. This is planned for the next year.

**Project title: Modeling Familial Co-aggregation of Congenital Heart Defects: An exploratory Data Analysis From the CHD Registry (RAC # 2070021)**

**Investigators:** M. Shoukri, S. Subhani, N. Dessouky, and M. Al-Joufan

### Introduction

Family studies are widely used for research into genetic and environmental influences on human traits. Study designs in which samples of family members are collected and compared with respect to their similarity have focused on single binary trait. However, the risk of co-occurrence of more than one disease in siblings of the same family is a parameter of interest to genetic epidemiologists and other investigators. For example, they may be interested in assessing the genetic and environmental etiologies of reading deficits (RD) and attention deficit hyperactivity disorder (ADHD) and their co-morbidity. In this proposal, we establish statistical methodology for the estimation of sib similarity with respect to two dichotomous traits measured on each member of the sib-pair. For inference problems involving a single sample, confidence intervals are discussed. For two sample problems (one sample of sibs taken from consanguineous marriages, and the other is taken from non-related marriages), several test procedures that account for the correlation between sibs and the correlation between traits are presented. The data will be extracted from the Congenital Heart Defects (CHD) registry supported by the Registry Core Facility (RCF) of the Department of Biostatistics and Epidemiology at The King Faisal Specialist Hospital and Research Centre.

### Objectives

1. For a sample of pairs of sibs, we test whether

similarity among them is the same for each of the two traits of Patent Ductus Arteriosus and Tetralogy of Fallot (PDA and TOF) and investigate their possible co-aggregation among siblings from the same family.

2. Evaluate the elevation of the risk of disease for a single sib conditional of the fact that the other sib has attained the same disease, accounting for the within cluster correlation.
3. We shall investigate the possible effect of consanguinity when two independent samples (related marriages and unrelated marriages) are made available. We compare the levels of similarities in a sample of unrelated marriages to that in an independent sample of related marriages. Significant differences are indications of possible genetic etiology.

Once the likelihood function of the model is constructed we:

1. Use the maximum likelihood estimation to estimate the model parameters.
2. Use the Delta method to derive the standard errors of the estimates.
3. Apply the theory of linear hypothesis testing to test the equality of the clustering parameters.

The project has just received approval from ORA on December 2007.

**Project title: Knowledge and awareness about cancer and its prevention; Attitude towards cancer preventive health behaviour" (RAC # 2051 041, KACST # MS 11-1).**

**Principal Investigator:** Dr. K. Ravichandran

**Co-Investigators:** Dr. Gamal-Eldin Mohamed, Dr. Nasser Al Hamdan, Mr. Abdallah Al-Rowais

#### Project description

Worldwide, there were over 1 0 million new cases of cancer and more than 6 million deaths from cancer by 2000. Although the disease has often been regarded as a problem principally of the developed world, in fact, of the 1 0 million new cancer cases annually, 4.7 million were in the more developed countries and nearly 5.4 million were in the less developed countries. Although much remains to be learned about the etiology of cancer, at least one-third of the cases are preventable by such means as controlling tobacco and alcohol use,

moderating diet, and immunizing against viral hepatitis B. Further one-third of cases can be controlled by early detection, and therefore prompt treatment, where resources allow.

Improved cancer control, to a substantial degree, relate to prevention strategies and early detection programme, including information campaigns and population-based screening programme. Success of these programmes depends largely on compliance of the targeted population, which in turn depends on awareness on cancer and attitude towards such programme. Lack of awareness may impede preventive efforts as well as the adoption of positive lifestyle changes. Earlier studies conducted in Saudi Arabia were few and limited to knowledge of and attitude towards breast cancer only. Further, one of the two studies was based on secondary school female students. The purpose of this study is to assess knowledge and awareness concerning cancer, early detection methods and attitude towards prevention programme in the Saudi Arabia.

#### Progress

This project was approved by KACST. Data collection team was trained in our department. Data collection is completed. Data entry is underway.

**Project title: Longitudinal Study of Prenatal and Postnatal Lead Exposure and Early Cognitive Development in Al Kharj, Saudi Arabia (RAC # 2031 050)**

**Investigators, Principal Investigator:** Iman Al-Saleh, Ph.D.

**Co-Investigators:** Gamal Mohamed, Ph.D, Stephen Schroeder, Ph.D, Abdullah Rabah, MD

#### Project description

Extensive data shows a direct link between low-level lead exposure during early development and deficits in neurobehavioral-cognitive performance evident late in childhood through adolescence. These consistent studies have demonstrated the presence of a constellation of neurotoxic and other adverse effects of lead at blood lead levels as low as 10 g/dl. Risk factors for prenatal exposure to lead involve maternal exposure and body burden of lead. There are both exogenous and endogenous factors contributing to maternal blood lead levels and in utero exposure to the fetus. Our previous study which investigated 124 pregnant women living in Riyadh revealed a strong

correlation between the maternal and cord blood lead levels confirming the transfer of lead from the mother to the fetus. This longitudinal study is designed to assess the effect of exposure to lead prenatally and postnatally on early cognitive development of infants living in a rural area such as Al-Kharj area where the use of traditional cosmetics and remedies is still common. Lead will be measured in 1000 umbilical cord blood samples collected from healthy pregnant women by means of Zeeman Atomic Absorption Spectrophotometer, coupled to Graphite Tube Atomizer. Based on their cord blood lead levels, infants will be classified into three groups for neuropsychological assessments: low lead exposure risk group (below the 10<sup>th</sup> percentile), medium lead exposure risk group (at approximately 50<sup>th</sup> percentile) and high lead exposure risk group (above the 90<sup>th</sup> percentile). Development will be assessed semi-annually, beginning at the age of 6, 12, 18 and 24 months, with the use of the Mental Development Index of the Bayley Scales of Infant Development. Venous blood samples will be obtained at the same times to provide a measure of postnatal lead exposure. We shall use a detailed questionnaire to gather basic socioeconomic, demographic, health and other risk factors for exposure to lead.

### Progress

Data collection and entry completed. A manuscript is prepared for publication

**Project title: Modeling Circadian Rhythms in Failure Time Data (RAC # 2060011)**

**Investigator: Principal Investigator:** Naser Elkum

### Project description

The human body has circadian rhythms that are coordinated with external time patterns. There are patterns that correspond to the daily wake/sleep cycle, a yearly seasonal cycle and, in women, the menstrual cycle. Sine/cosine functions are often used to model circadian patterns for continuous data, but this model is not appropriate for analysis of circadian rhythms in failure time data. A method will be presented to provide an estimate and confidence interval of the day where the minimum hazard is achieved. The model will be used to predict the optimal day in the menstrual cycle for surgery (i.e. day associated with the lowest recurrence rate) in pre- menopausal breast cancer.

### Progress

The project has been successfully completed and the final report has been submitted to RAC. A paper has been published in *Journal of Circadian Rhythms*.

**Project title: Cellular and Molecular Characterization of Medulloblastoma in Saudi Patients: Correlation with Prognosis and Therapy (RAC # 2050 016)**

**Principal Investigator:** Abdelilah Abousekhra

**Co-Investigator:** Naser Elkum

### Project description

Cancer is a multi-stage complex genetic disease that can develop in different organs and cell types. Brain tumors represent 4.6% of the total cancer cases in the KSA and 35% of these cases are patients under 9 years old, making the brain tumors the second most common pediatric cancer. Medulloblastoma that arises in the cerebellum, is the most common pediatric primary malignant brain tumor. Since the Saudi population is young with the majority of the citizens under 20 years of age, a more precise understanding of the cellular and molecular basis of medulloblastoma is clearly necessary in order to improve the treatment of this cancer by facilitating the objective of matching therapy to tumor biology.

Therefore, our main objective is to establish and characterize cell lines from medulloblastomas derived from Saudi children and try to identify molecular markers that could be correlated with prognosis and hence can be used as a disease-risk stratification tool.

To achieve this goal, we will analyze the status and expression levels of different genes including the MYC oncoprotein, the tumor suppressor TP53-ARF pathway, the receptor tyrosine kinase TRKC oncoprotein and the protein kinases Aurora A and B. Finally, we would attempt to correlate these with the cellular and tumor responses to the therapeutic agents used in the treatment of medulloblastoma, and with the treatment outcome.

The resulting findings will allow the combination of clinical and molecular diagnostic markers, which will lead to:

- Accurate disease-risk assignment for children with medulloblastoma

- Better management of medulloblastoma patients based on the molecular profiling of the tumor
- Reduce the treatment intensity in low-risk group without compromising the cure rate and to develop more effective treatment for children with resistant disease
- Determine a combination of clinical and molecular prognostic variables that may improve disease-risk classification of medulloblastoma.

#### Progress

RAC approved the project and tissue collections are in progress. No statistical analysis done yet.

**Project title: Efficacy of Combination Therapy with PEG- Interferon Alfa-2a (pegasys) Plus Ribavirin in the Treatment of Chronic Hepatitis C. (RAC # 2051035)**

**Principal Investigator:** H. Al-Ashgar  
**Co-Investigators:** K. Alsawat & N. Elkum.

#### Project description

With the introduction of current standard therapy for chronic HCV using pegylated interferon combined with ribavirin, This study aims to evaluate the response rate in our patients with chronic HCV who had been treated with this regimen (combination of pegylated interferon alfa-2a (Pegasys, Roche Pharm aceuticals) and Ribavirin).

#### Progress

The project has been successfully completed and the final report has been submitted to RAC. Two papers have been submitted for publications. Two abstracts have been presented in local Saudi society of gastroenterology and one in Asian specific association of APSL Japan.

**Project title: Efficacy of Peginterferon  $\alpha$ -2a in Hbe Ag Negative Chronic Hepatitis B: Naïve versus Lamivudine Resistance Patients". (RAC- # 2051045)**

**Principal Investigator:** H. Al-Ashgar  
**Co-Investigators:** K. Alsawat & N. Elkum.

#### Project description

This is a prospective, randomized, open label, multicenter study comparing the efficacy and safety of peg interferon  $\alpha$ -2a (40 kDa), in HbeAg negative chronic hepatitis B

naïve and lamivudine resistance Saudi patients who fulfilled all the inclusion and exclusion criteria. The study will be conducted at 6 different major hospitals in Riyadh: KFSH&RC, Security Force Hospital, National Guard Hospital, Military Hospital, Riyadh Central Hospital, and King Khalid University hospital. Sixty-five patients, who met all the inclusion and exclusion criteria, will be included in the study for the next 1-year and the study will be completed after 96 weeks of last patient enrollment.

#### Progress

Due to the slow rate of recruiting patients of this study, only thirty-five patients have been joined the study. RAC has approved an extension of this project until June 2008. Pharmaceuticals Hoffmann- La ROCHE funds the project and patient recruitments are ongoing.

**Project title: Pathogenesis of Early Infantile Primary Lactic Acidosis. (RAC Project # 2050-009)**

**Investigators:** Kaya N, Al-Owain M, 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. For the microarray analysis we will be using ABI 1700 system to determine the gene signatures in whole blood and identify key genes likely to participate in the apoptotic and nuclear/mitochondrial dialogue for this disease.

#### 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 Microarray system. Initial data analysis was performed by using R/Bioconductor, Matlab, and other publicly and commercially available 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.

## TECHNICAL SUPPORT AND DATA ANALYSIS: COLLABORATIVE RESEARCH

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**Project title:** Mitral Balloon Valvotomy - Immediate and Long Term Effect. (RAC #: 2001 054)

**Principal Investigator:** Mohammed Fawzi, MD  
**BRU Investigator:** Abdelmoneim Eldali  
**BESC #:** 011/1995

### Project description

Mitral balloon valvotomy is an established non-surgical modality for the treatment of severe mitral valve stenosis. Although in children and adolescents with mitral stenosis the immediate and midterm hemodynamic effects of balloon valvotomy have been adequately documented, there is a paucity of data regarding the long-term results of mitral balloon valvotomy in this age group. This project aims to analyze the data of 365 patients with mitral stenosis who were submitted to mitral balloon valvotomy in our institution and to follow up.

The objective is to assess the safety, efficacy and long-term results of mitral balloon valvotomy in children and adolescents in comparison to adults.

### Progress

Data analysis phase. Several publications and presentations resulted from this project.

**Project title:** Study, Using a Baboon Model, of the Coagulation Response Patterns to Severe Heat Stress and its Relation to Inflammation and Cell Injury. (RAC # 2002 067)

**Principal Investigator:** Abderrezak Bouchama, MD  
**BRU Investigator:** Abdelmoneim Eldali

### Project description

Heatstroke is associated with massive activation of coagulation leading to microvascular thrombosis in various organs, and death. Knowledge of the molecular mechanisms responsible for this activation of coagulation in heatstroke is important for the development of new modalities of treatment. Using a baboon model of heatstroke, we propose to test the hypothesis that (1) cellular injury and death in heatstroke are the result

of disseminated intravascular coagulation initiated by the expression of tissue factor, and (2) that blocking the activation of coagulation either by a tissue factor pathway inhibitor (TFPI) or recombinant activated protein C reduce significantly the coagulopathic and lethal effects of heat. Four baboons are heat stressed to a rectal temperature of 43.5°C (LD100 heat at 48 hours) in a modified neonatal incubator where the environmental temperature is maintained at 47°C. The animals are monitored for vital signs, and the concentrations of coagulation (thrombin-antithrombin complexes, soluble fibrin monomers, D- Dimers, tissue factor) and fibrinolysis components (plasmin-antiplasmin complexes, tissue plasminogen activator and plasminogen activator inhibitor) and inflammatory mediators (TNF, IL-1, IL-6, IL-10) at T=15 minutes during heat stress and T=1, 6, 24, 48 hours during recovery/progression of injury. Four sham-heated baboons will serve as a control group. Survival at 3 days will be compared between each group.

### Progress

Data analysis completed for phase I, II, and III. Several publications and presentations resulted from this project.

**Project title:** Gulf Center for Cancer Registration (RC Admin Approved, BESC# 032/2001)

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

### Project description

The Gulf Center for Cancer Registration (GCCR) was established in 1997. The GCCR works under the jurisdiction of the Executive Office for Ministries of Health Council of GCC countries. The main office is located in the premises of the Research Center, King Faisal Specialist Hospital and Research Centre. The GCCR database, population-based incidence data that include information on both benign and malignant primary tumors, is of the largest aggregations in Asia. Compiling data from the six national cancer registries representing the six Gulf countries: Kingdom of Bahrain, Kingdom of Saudi Arabia, State of Kuwait, State of Qatar, Sultanate of Oman and United 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. The National Cancer Registry in each country is responsible for the data collection at the national level from health facilities that diagnose or treat cancer in that country. Data which include patient's identification, demographics information, site of cancer, histology, stage of the disease, etc. are collected from the patient's medical records based on clinical and histological diagnosis. Collected data will be sent to GCCR main office for ensuring the accuracy of information reported and subsequently for annual data analysis.

### Progress

The population pyramid for each GCC country was produced in SAS® for the GCCR Annual/Cumulative Report 2007.

### **Project title: Thromboembolic Disorders Registry (TEDR) (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

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a significant cause of morbidity and mortality all over the world. Deep vein thrombosis (DVT) affects primarily the veins of the lower leg and thigh. A thrombus forms in a proximal vein, blocking the flow of blood and often (but not always) causing swelling and inflammation. While deep vein thrombosis is not life threatening, the thrombus can break free and travel to the pulmonary artery or one of its branches and block pulmonary blood flow, leading to pulmonary embolism (PE), the most serious sequela of DVT. The Thromboembolic Disorders Registry of King Faisal Specialist Hospital and 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. All patients presenting to the Thromboembolic Service in the section of Internal Medicine are registered. However only those who understand, accept and sign the Informed Consent Forms are included in the registry.

### 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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the TEDR Annual/Cumulative Report 2007.

### **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

SAS® programs have been written for data analysis and presentation for the CLPR Annual/Cumulative Report 2007.

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

#### **Progress**

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the Epilepsy Registry Annual/Cumulative Report 2007. Technical support was provided when needed.

**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 determine the types of neuromuscular diseases found in the population. Moreover, to obtain the 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**

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the NMDR Annual/Cumulative Report 2007. Technical support is provided when needed.

**Project title: Congenital Heart Disease Registry (RAC# 991 026, BESC# 011/96)**

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

#### **Project description**

Congenital heart defect (CHD) is an inborn anomaly due to unknown causes and is an important cause of infant mortality and morbidity. CHD is defined as a gross structural abnormality of the heart, great vessels or the conduction system that is actually or potentially of functional importance. Studies of the incidence of this disease in populations provide different incidence rates. The congenital heart defects registry of the King Faisal Specialist Hospital and Research Centre (KFSH &RC) started in 1998 as 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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the CHDR Annual/Cumulative Report 2007.

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

### Progress

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the NTDR Annual/Cumulative Report 2007. Technical support is provided when needed.

**Project title: National Diabetes Registry (RC Admin Approved, BESC# 028/2001)**

**Investigators:** Al Rubeaan K, Al Ageel S, Subhani S, Hashim S

### Project description

Diabetes mellitus (DM) is a major and growing problem in the Kingdom of Saudi Arabia causing prolonged ill health, disability, early death and high health cost. Diabetes being a chronic disease causes chronic complications with high morbidity and mortality rate. To monitor this

disease in the Kingdom of Saudi Arabia, a National Diabetes Registry was established in 1996. The DM registry will help in having better knowledge on the geographic distribution, the demographic characteristics and the clustering of DM in families. The DM registry will serve as an easily accessible source for data on Saudi diabetics. This will encourage researchers to study the problem of DM in the Kingdom. The aggregation, analysis and presentation of information about DM is expected to significantly contribute to the medical understanding, demonstrating trends in management, improving the quality of care for DM patients and supporting planning and development.

### Progress

Tables, graphs and charts have been produced in SAS® for the purpose of generating the Diabetes Registry Cumulative Report.

**Project title: PCR Assay For Detection And Quantification Of Fungal Infections In Pediatric Patients With Acute Myeloid Leukemia And Myelodysplastic Syndrome. (RAC # 2021 054)**

**Investigators:** Rajeev K. Sathiapalan, Ibrahim Bin-Hussain, Rong Bu, Asim Belgaumi, Mohammed O. Qutub, Ahmed Al-Ahmari, Faisal Al-Kurdi, Edna Almodovar, Wilhelmina Ventura

### Project description

Fungal infections pose a serious challenge to survival of the child with cancer by its life-threatening nature and also compromising definitive treatment of underlying disease. Novel methods for early detection of fungi include polymerase chain reaction (PCR), galactomannan antigenemia, antibody titers and detection of fungal metabolites. Although PCR-based assays targeting unique DNA sequences have been developed for detection and identification of *Candida* and *Aspergillus* species, their application to patients at high risk for invasive mycoses is still in infancy.

A significant number of children with cancer treated at KFSH&RC and KFNC&RC develop fungal infections for unknown reasons. This longitudinal, prospective study aims at early detection of fungi by PCR assay as a surrogate marker of invasive fungal infection in pediatric patients with acute myeloid leukemia and myelodysplastic syndrome treated on acute myeloid leukemia protocol. It is expected to complement the different strategies

for reducing the morbidity and mortality from fungal infections.

### Progress

Data has been collected for 19 patients excluding the monitoring data of PCR with and without anti-fungal treatment. The database was created in SPSS and preliminary tables were submitted to Dr. Ibrahim Bin-Hussain.

**Project title: The Use Of Chlorhexidine Oral Care For The Prevention Of Ventilator-Associated Pneumonia (VAP). (RAC # 2021 076)**

**Investigators:** Mohammed Hijazi, Wilhelmina Ventura

### Project description

Despite advances in the field of critical care and infection control, nosocomial pneumonia continues to be a major cause of morbidity and mortality among patients requiring mechanical ventilation and a common source of controversies among their care providers about the best diagnostic, preventive and therapeutic strategies.

Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections in intensive care units. VAP continues to complicate the source of 8 to 28% of patients receiving mechanical ventilation (MV) with mortality rate ranges from 24 to 50% and can reach 76% in some specific settings or when lung infection is caused by high-risk pathogens.

Chlorhexidine is an antiseptic solution that has been used by dentists since 1959 for the control of dental plaque. It is rapidly bactericidal to both gram-positive and gram-negative bacteria and yeast. Chlorhexidine has been studied extensively and shown to decrease aerobic and anaerobic bacteria in the oral cavity from 55 to 97% without any significant changes in bacterial resistance, overgrowth of potentially opportunistic organisms or other adverse changes in the oral microbial ecosystem.

Oral care is performed in all critically ill intubated patients. In our ICU, as in most ICUs, normal saline is used by the nurses for routine oral care. No studies evaluated the use of chlorhexidine-based oral care in the prevention of VAP in medical and non-cardiac surgical critically ill patients. Preventing VAP in this high risk group using a simple and cost effective intervention will lead to fewer

days in the ICU, less antibiotic use, less cost and possibly less mortalities.

The objective of the study is to compare oral care using chlorhexidine to the routine oral care on the occurrence of VAP in mechanically ventilated medical and surgical critically ill patients.

### Progress

Data for 346 patients were collected for this study but only 242 cases were included when the exclusion criteria were applied. Final data management activities and statistical analysis were done. This study is completed.

**Project title: Identification Of Environmental And Genetic Factors That Influence Breast Cancer Development And Therapy In Saudi Females. (RAC # 2031 091, KACST # ARP-2432)**

**Investigators:** Nasser El Kum, Wilhelmina Ventura

### Project description

The cancer data of the Kingdom of Saudi Arabia show that breast cancer is hitting the largest proportion of the female population of the cancer patients. The high incidence and mortality rates for this type of cancer may be attributed to a number of risk factors which are to be explored for the Saudi population. We found in the Western literature that the factors showing significantly higher risks are: age at presentation; family history of breast cancer, cervix, uterus, or colon; age at first pregnancy after thirty; history of previous breast cancer, early menarche and late menopause; excessive radiation; and obesity.

Because of the lack of any original data on this subject in the Kingdom of Saudi Arabia, a case-control study is planned to be conducted at national level. This research study will describe the risk factors of breast cancer and the relationship among these factors for the Saudi population, thus, giving a better understanding of this disease in this part of the world. On the basis of this research, attempts can be made to lower both the incidence and mortality rates of breast cancer.

### Progress

Data for 1255 patients and 707 controls has been collected and entered in an MS Access database. Data collection is ongoing.

**Project title: Prevalence Of Anemia And The Transfusion Practices In Critically Ill Patients. (RAC # 2031 018)**

**Investigators:** Khalid Al Maghrabi, Rasheed Al Hubail, Mohammed Hijazi, Nabila Abouchala, Torbjorn Wetterberg, Gamal Mohammed, Wilhelmina Ventura

#### **Project description**

Anemia is common in critically ill patients. By day 3 of intensive care unit admission, about 95% of the patients have hemoglobin concentration below normal. Blood transfusion and blood conservation are complementary activities that constitute the clinical arena of transfusion medicine. Recent improvement in the safety of the blood supply and the increasing costs associated with transfusion therapies have led to a reevaluation of the clinical practices of blood transfusion and blood conservation.

The transfusion practice in ICU patients is variable and the current transfusion guidelines may not be suitable for critically ill patients. The rate of transfusion in ICU ranges from 4% to 66% with an average transfusion rate of 44%. The rate of transfusion will increase with increasing length of stay in ICU. Hebert PC et al in the TRICC trial demonstrated that using transfusion trigger of 7 gm and maintaining hemoglobin concentration between 7.0-9.0 gm/dl in normovolemic patients is at least as effective as and possibly superior to a liberal transfusion strategy in which a transfusion trigger of 10.0 gm/dl and hemoglobin concentration were maintained at 10.0-12.0 gm/dl were used. With the exception of patients with acute myocardial infarction and unstable angina, using a restrictive strategy of red blood cell transfusion demonstrated a reduction in the total transfusion and decreased the chance for exposure to blood products, which carry a great importance in the presence of donor shortage and variable multiple risks associated with transfusion.

#### **Progress**

Data for 450 patients were collected, but after application of the exclusion criteria, 6 patients were excluded. Data were entered into Excel files which were later converted into SAS. Frequency tables were generated. Statistical analysis will follow.

**Project title: Disseminated Fungal Infections Among Pediatric Patients 0-14 Years of Age with Hematological**

**Malignancies at KFSH&RC: A Prospective Study. (RAC #: 2041 006)**

**Investigators:** Ali Al-Ahmari, Ibrahim Bin-Hussain, Gamal Mohammed, Wilhelmina Ventura

#### **Project description**

Invasive fungal infections are more prevalent than ever, presenting an enormous challenge to healthcare professionals. This prevalence is directly related to the growing population of immunocompromised individuals resulting from changes in medical practice such as the use of intensive chemotherapy and immunosuppressive drugs. In the hospital, complicated surgical procedures, widespread use of implanted devices, and the administration of a broad spectrum of antibiotics have dramatically increased the incidence of nosocomial bloodstream infections. Systemic fungal infections are a main cause of morbidity and mortality in patients with hematological malignancies.

#### **Progress**

A 10-page data collection form has been finalized. Data for 108 patients were collected. Data were entered into an MS Access database. Data cleaning and validation are ongoing.

**Project title: Efficacy Of Combination Therapy With PEG-Interferon  $\alpha$ -2a (Pegasys) Plus Ribavirin In The Treatment Of Chronic Hepatitis C: Retrospective Study. (RAC #: 2051 035)**

**Investigators:** Hamad Al Ashgar, Khalid Alsawat, Nasser El Kum, Mohammed Qaseem Khan, Saleim Dahab, Mohammed Al Fadda, Ingvar Kagevi, Wilhelmina Ventura

#### **Project description**

Infection with Hepatitis-C virus (HCV) can result in both acute and chronic hepatitis. Acute infection is usually asymptomatic, rarely leads to hepatic failure but typically leads to chronic infection in 60-80% of cases. Chronic HCV infection is usually slowly progressive; the most common cause of chronic liver disease and the most frequent indication for liver transplantation in some parts of the world. Approximately 20-30% of chronically infected individuals develop cirrhosis over a 20 to 30-year period of time.

In Saudi Arabia the estimated seroprevalence of HCV in community-based study is estimated 1.8% similar result of 1.1% in blood donors, however, surprisingly higher prevalence in hemodialysis patients at 55-68% in one report. Genotype 4 is predominant in the Middle East and Africa.

Given data from previous studies regarding treatment of chronic HCV infection and the presence of little information in the literature with regards to genotype 4 treatment, we plan to study the experience in our hospital in the treatment of chronic HCV. It will also include demographic and virology data for this infection.

With the introduction of the current standard therapy for chronic HCV using pegylated interferon combined with Ribavirin, we will evaluate the response rate of patients with chronic HCV.

#### Progress

A 3-page data collection form has been finalized. Data collection is ongoing.

**Project title: Fever Of Unknown Origin: Experience Of A Tertiary Care Center In Saudi Arabia. (RAC #: 2061 009)**

**Investigators:** Mahmoud A. Moawad, Habib Bassil, Mona Elsharif, Mostafa Elnaggar, Jameela Edathodou, Ibtisam Baksh, Wilhelmina Ventura

#### Project description

Fever of unknown origin (FUO) is defined as a temperature higher than 38.3 degrees centigrade on several occasions and lasting longer than 3 weeks, with diagnosis that remain uncertain after 1 week of investigation in hospital or in outpatient setting. The condition represents a diagnostic challenge and as such constitutes a significant number of referrals to tertiary care centers. Previous studies have described the spectrum of the disease to be mainly secondary to infectious, neoplastic or inflammatory diseases. Between 9% and 30% in different studies end up without diagnosis despite exhaustive workup. The prognosis of these patients was found to be generally good. Occasionally, deep vein thrombosis (DVT) can present as FUO.

Diagnostic workup that starts with confirming the presence of fever in hospital and emphasizing that there is no "gold standard" test that exists for these patients is well described. Suggested minimal diagnostic workup

to qualify as FUO include: complete H&P including drug history, CBCD, blood film, routine blood chemistry, urinalysis and microscopy, blood x 3 and urine cultures, ANA, RF, HIV, CMV IgM antibodies, heterophil antibody test (if consistent with mononucleosis-like syndrome), Q-fever serology (if exposure risk factors exists), CXR, hepatitis serology (if liver enzymes elevated). The role of different nuclear medicine studies (e.g. labeled leukocytes, gallium, Indium & Technitium scans) was emphasized in these patients, especially in ruling-out inflammatory conditions. In one study, immunoscintigraphy with monoclonal antibody 99mTc-BW/250/183 sensitivity in detecting pyogenic foci was 73% and specificity was 97%, positive and negative predictive values were 93% and 87%, respectively.

With the exception of one study from Turkey, no local information is available about FUO in the Middle East. Reporting our experience should fill some of this literature gap and might be of help to our colleagues when they are faced with a patient with FUO.

#### Progress

A 5-page data collection form has been finalized. Data collection is ongoing.

**Project title: Signaling Pathways Involved In Heatstroke Pathogenesis: Role Of Toll-Like Receptor-4 (TLR-4). (RAC #: 2060 013)**

**Investigators:** Mohammed Dehbi, Taher Uz-Zaman, Abderrezak Bouchama, Mohammed Dehbi, Engin Baturcam, Steve Bobis, Moahamed Hassan, Sahar Salem, Ludivina Apilado, Abdelmoneim Eldali and Wilhelmina Ventura.

#### Project description

In this project, we will be focusing on the molecular mechanisms governing the inflammatory, tissue injury and death responses associated with heatstroke using a mouse model. Our initial work is primarily emphasized on the role of TLR-4, a key component involved in various inflammatory responses such as sepsis, shock, burn, trauma, tissue injury and microbial infection, particularly to specific microbial components such as the endotoxin lipopolysaccharide (LPS). Our working hypothesis was based on the observation that heatstroke was associated with a release in the circulation of LPS. In addition, blocking the effects of LPS by administration of anti-lipopolysaccharide agent was shown to improve animal

survival from heatstroke effects. These observations prompt us to raise the question as to whether LPS triggers or potentiates the inflammatory response observed in heatstroke cases. In an attempt to dissect this relationship, we took advantage of the availability of LPS-resistant C3H/HeJ mice, an inbred strain that resists the LPS effects due to a mutation in TLR-4. The wild type strain C3H/HeOuj is used as control.

For each strain, animals were randomly divided into 2 groups: sham-heated group, heatstroke group. Blood and tissue samples will be collected at the onset of heatstroke and at various time points during the recovery period. Expression profiling of a panel of pro-inflammatory and anti-inflammatory mediators will be monitored. Survival rate will be established.

### Progress

A 2-page data collection form has been finalized. Except for the experimental data items, study data has been collected for 141 patients. Of these, 129 are included in the study while 12 were dropped due various reasons, i.e. low body temperature, underweight, died, etc. Data were entered into an SPSS database. Data collection is ongoing.

**Project title: Neuropsychology Study (RAC #: 2061 080)**

**Investigators:** Ahmed M Hassan, Wilhelmina Ventura

### 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 of which are MRI, PET, EEG, and Neuropsychological Evaluation. Agreement among those 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

An SQL database has been created by BESC for this study. The principal investigator himself enters the data into the database. Presently, there are 222 cases in the database. Data has been converted into SAS and SPSS for the PI to do preliminary analysis.

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  - Alsmadi O, Al-Rubeaan K, Wakil SM, Imtiaz F, Mohamed GH, Al-Saud H, Al-Saud NA, Aldaghri N, Mohammad S, Meyer BF. Genetic Study of Saudi Diabetes (GSSD): significant association of the KCNJ11 E23K polymorphism with type 2 diabetes. *Diabetes Metab Res Rev.*, 2007
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- #### Published Abstracts
- Elkum N, Dermime S, Ajarim D, Al-Zahrani A, Alsayed A, Tulbah A, Almalik O, Al-shabana M, Ezzat A and Al-Tweigeri T. "Age 40 and younger is an independent risk factor for relapse in operable breast cancer patients: The Saudi Arabia experience." Presented at 7<sup>th</sup> Scientific Meeting of the International Epidemiology Association-EMR, KFHS&RC, Nov 27 - 29, 2007.
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#### **Abstracts/presentation**

- Mohamed GH, Shoukri MM and Dzimiri D. Gene-environment interaction between diabetes mellitus type 2 and E-selectin S128R mutation in coronary heart disease manifestation: a propensity score approach. 7<sup>th</sup> Scientific Meeting of the International Epidemiology Association. Eastern Mediterranean Region . 27-29 November 2007. Riyadh-Saudi Arabia
- Fawzy ME, Shoukri MM, Al Buraiki J, Al Shahid M, Kharabsheh S, Al Widaa H, Eldali A, Al Sanei A, Canver C. 17 Years Clinical and Echocardiographic Follow-Up Results of Mitral Balloon Valvuloplasty in 520 Patients of Long-Term Outcome. American College of Cardiology 56<sup>th</sup> Annual Scientific Session, March 24-27, 2007, New Orleans, Louisiana, USA.

## Research Unit

# EPIDEMIOLOGY

The Epidemiology Research Unit (ERU) within the department of Biostatistics and Epidemiology, at the King Faisal Specialist Hospital and Research Center (KFSH&RC) encompasses a broad range of research focus, including cancer, diabetes, nutrition and women's health. The unit is dedicated to understand the patterns and causes of health and disease, and the application of that knowledge in improving the health of populations. ERU maintains close collaborative ties with number of other departments in KFSH&RC. The unit also has strong links to other institutions and programs, including Ministry of Health, Prince Salman Center for Disability Research (PSCDR), and the Saudi Commission for Health Specialities.

Currently, the unit has 4 permanent and 2 adjunct scientists and 6 technical staff members (4 permanent and 2 grant positions). They focus their research efforts on community-based and hospital-based epidemiological studies on cancer, nutrition and reproduction. Several studies were being designed and implemented by the ERU scientists and technical staff. Members of the ERU were actively involved in 13 RAC approved studies during 2007. Results of these studies has often been published in peer reviewed journals and were presented in national and international conferences.

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### **Head:**

**Ali Al-Zahrani, MD, PhD**

### **Members:**

Abdulaziz Al-Othaimen

Yasmin Al-Twajiri

Ravichandran Kandasamy

Saud Al-Shanafey (adjunct)

Abdullah Al-Joudi (adjunct)

Abdulrahman Bin Muammar

Amal Al-Madouj

Wiaam Al-Obaid (December 2007)

Batlah Al-Marshad

Asia Khalifa

Saud Al-Rowaily (March 2008)

## RESEARCH PROJECTS

**Project title: Gulf Center for Cancer Registration (GCCR) (BESC# 002 2006 RAC# 2061 022)**

**Principal Investigator:** Dr. Ali Al-Zahrani

**Co-Investigators:** Dr. Kandasamy Ravichandran, and Mis. Amal Al-Madouj.

### Project description

The Gulf Center for Cancer Registration (GCCR) was established in 1997 to create a cancer incidence database for the Gulf Cooperation Council (GCC) countries. The GCCR database, which is population-based and includes information on both benign and malignant primary tumors, includes data from the national cancer registries of the GCC states: United Arab Emirates, Kingdom of Bahrain, Kingdom of Saudi Arabia, Sultanate of Oman, State of Qatar and State of Kuwait.

### Progress

The total number of incidence cancer cases registered among GCC nationals from January 1998 to December 2004, were 62,814 (Male 31,348; Female 31,466). Almost half of the cancer cases had either regional or distant metastasis at the time of diagnosis. Only one fifth of patients presented with localized tumors and less than 2% with in situ. In general, age specific incidence rates for all cancers increase with age in both genders. Almost 71% of cancer cases were among Saudi nationals, 12% were Omanis, 7% were Kuwaitis, 5% were Bahrainis, 4% were from the UAE, and 2% were Qataris.

Breast cancer is the most common cancer in the GCC States accounted to 11% from all cancers and 22% from cancers among females. Non-Hodgkin's Lymphoma (NHL) and Leukemia are the second and third most common cancer in the GCC States followed by colorectal and Thyroid cancers. Liver cancer ranked second most common cancer in men next to NHL, whereas thyroid cancer ranked second in women next to breast cancer. In children, leukemia appeared to be the leading cancer followed by cancer of the brain and nervous system, Hodgkin disease, and non-Hodgkin's lymphoma.

- An original article entitled " Association of Reproductive Factors with the Incidence of Female Breast Cancer in the GCC Countries" was accepted for publication by EMHJ.

- Cervical cancer screening with pattern of Pap smear. Review of multicenter studies. - Correspondence - Saudi Med J. 2007; 28(8): 1305.
- Epidemiology of thyroid cancer: A review with special reference to Gulf Cooperation Council (GCC) States. The Gulf Journal of Oncology. 2007; 2: 17-28.
- 2003 Cancer Incidence Report for the Gulf Cooperation Council Countries. Riyadh: Gulf Center for Cancer Registration, 2007.
- Association of reproductive factors with the incidence of female breast cancer in the GCC States. Abstract in the 7<sup>th</sup> IEA Eastern Mediterranean Regional Scientific Meeting at Riyadh, Saudi Arabia. November 2007 (Abstract Book P59).

**Project title: Validation of the Arabic Symptom Assessment Scale (RAC#2061 049)**

**Principal Investigator:** Dr. Mohamed Al Shehri, and Dr. Ali Al-Zahrani

**Co-Investigators:** Dr. Mohamed Shoukri, and Dr. Samy Al-Sairafy

### Project description

Symptom management is one of the main fundamentals of Palliative Care. One can not overemphasize that proper assessment is a prerequisite for optimal symptom control. Valid and reliable assessment tools are also essential for measuring treatment outcomes. Symptoms are subjective uncomfortable feelings that are difficult to precisely quantify and are best described by the individual patient. However, various tools have been developed to standardize the symptom assessment methods. The investigators in this project believed that there is a need to have a valid and reliable symptom assessment tool in Arabic language that satisfies the following criteria: acceptable level of validity and reliability, coverage of the most common symptoms among palliative care target population, mainly patients with far advanced, incurable and life threatening diseases, and ease of administration and completion given the sick and vulnerable nature of the palliative care population.

To the best of the investigator's knowledge, no such instrument exists so far. The objectives of this project are to test the validity and reliability of the Arabic Symptom Assessment Scale (ASAS) in assessing ten common symptoms among palliative care patients, and to describe the extent of contribution of various symptoms on the ASAS to the overall suffering experienced by the patient,

**Progress**

Data collection on progress.

**Project title: External Pressure Compression for Umbilical Hernia Management: Randomized Clinical Trial (RAC# 2071 070)**

**Principal Investigator:** Dr. saud Al-Shanafey

**Co-Investigators:** Dr. Ali Al-Zahrani, Dr. Abdullah Al-Dowaish, Dr. Fahad Al-hazzani, and Dr. Saleh Al-Olayan.

**Project description**

Umbilical hernia is one of the most common abnormalities that affect infants. Although most physicians believe that umbilical hernias close spontaneously, few studies have documented the natural history of this condition. Few studies have attempted to test the utility of the external compression for the management of infantile umbilical hernia. We hypothesize that use of external compression promote early closure of the fascial defect in umbilical hernia patients. A randomized clinical trial design will be utilized. Infants younger than 6 months of age diagnosed with umbilical hernia will be randomized to either external pressure compression (group A) or expectant management (group B). Group A patients will have a compressive dressing applied over the umbilical hernia. The dressing will be changed every 48 hours. All patients will be followed up at 3 and 6 months after recruitment. Groups will be compared regarding the decrease of fascial defect, closure of fascial defect, and development of complications. Descriptive statistics will be generated for each group and compared. Means will be compared using student t-test, and proportions will be compared using Chi-square or Fisher's exact test where appropriate.

**Progress**

This project was approval by RAC and data collection on progress.

**Project title: Prospective Evaluation of Risk-Adapted Therapy for Pediatric Patients with Non-Lymphoblastic Non-Hodgkin Lymphoma (PEDNHL04-1) (BESC# 021 2004 RAC# 205 1018)**

**Principal Investigator:** A. Belgaumi

**Co-Investigators:** A. Al Kofide, R. Sabbah, Y. Khafaga, MA. Iqbal, W. Mourad, K. Ravichandran, K. Siddiqui,

L. Osman

**Project description**

Non-Hodgkin's Lymphoma constitutes a significant proportion of the malignancies seen during the pediatric age. The exact percentage is highly variable within different geographic regions, accounting from 10-13% in North America, to almost 50% in Equatorial Africa. Despite this variability in incidence, the range of pathologic subtypes of NHL in the pediatric age group is quite restricted, when compared to the adult age group. By far, the majority of children with NHL develop high-grade lesions that are aggressive, and occur predominantly in extranodal sites.

Over three decades ago, it was realized that pediatric NHL as a group was a highly chemosensitive entity. Chemotherapeutic regimes have since been developed that have resulted in an extremely good outcome for children with this malignant disorder. Currently, with intensive, multi-agent chemotherapy protocols, over 90% of patients with limited stage disease, and between 65-85% patients with advanced disease, can expect to be cured. The wider range of cure rates seen for the advanced stage disease is a reflection of the differing response of the different histologic subtypes, and the overall poorer prognosis of patients with CNS disease.

**Progress**

Patient accrual continued in 2007. Dialogue has been initiated with the pediatric oncology team at the National Guard Hospital, Riyadh, for potential collaboration on this study.

**Project title: Knowledge, Awareness and Attitude About Cancer and Its Prevention (BESC# 017 2005 RAC# 205 1041)**

**Principal Investigator:** Dr. K. Ravichandran

**Co-Investigators:** Dr. Gamal El din Mohamed, Dr. Nasser Al-Hamdan

**Project description**

Lack of awareness may impede preventive efforts as well as the adoption of positive lifestyle changes. Knowledge about cancer may influence care-seeking behavior, participation in treatment decision-making, as well as in primary and secondary prevention. Understanding perception of cancer risk can enhance the development of

screening interventions to maximally reach by addressing culturally based perceptions. Earlier studies conducted in Saudi Arabia were few and limited to knowledge of and attitude towards breast cancer only.

The purpose of this study is to assess knowledge and awareness concerning cancer, early detection methods and attitude towards its prevention programme in Saudi Arabia.

### Progress

An interviewer, using a structured questionnaire, obtained the required information from randomly selected individuals among the primary health care unit attenders. An informed oral consent was obtained before the interview. Computerisation of the responses to socio-demographic characteristic, awareness on cancer and attitude towards early detection methods are in progress.

**Project title: Cleft Lip/Palate (CL/P) and Craniofacial Anomalies Registry (BESC# 007 1999 RAC# 991 030).**

**Principal Investigators:** Dr. A. Al-Johar and Dr. K. Ravichandran

**Co-Investigators:** Mrs. Shazia Subhani.

### Project description

The King Faisal Specialist Hospital and Research Centre (KFSH&RC) established a CL/P registry and started collecting data on CL/P patients attending the KFSH&RC since mid-1999. The registry is a coordinated collaboration between the Department of Dentistry and Department of Biostatistics, Epidemiology and Scientific Computing. The CL/P registry is expanded in year 2002 to include Craniofacial Anomalies in its scope and hence the name of the registry is being changed from Cleft Lip/Palate Registry to "Cleft Lip/Palate and Craniofacial Anomalies Registry".

### Progress

A report, 'Cleft Lip/Palate and Craniofacial Anomalies: Annual Report 2006' was published. In 2006, this registry registered a total of 62 cases. There is a reduction of 47 cases (43.1%) in 2006, compared to previous year (n=109). The reduction is mainly due to changes in eligibility criteria on patient acceptance in KFSH&RC. Out of the 62 cases 42 (67.7%) cases had

only cleft of lip and/or palate, 7 (11.3%) cases had only cranial/facial anomalies and 13 (21.0%) cases had both CL/P and CF anomalies. There were 39 males and 16 females of CL/P cases with the male to female ratio of 2.4:1. Bilateral cleft lip and palate was common followed by unilateral cleft lip and palate. Out of the 20 craniofacial anomalies 16 were male and 4 were female with a male to female ratio of 4:1. Among craniofacial anomalies 60% of the cases had only facial (n=12), 30% had only cranial (n=6) and 10% had both the anomalies (n=2).

Riyadh region had more number of cases (n=19; 30.6%) followed by Asir (n=10; 16.1%) and no cases were reported from both Hail and Najran region. The primary surgeries like initial lip & nose repair, initial palate repair accounts to 14.2% and 8.0%, respectively, of the total procedures (225) done. About 40% of these surgeries (n=20) were done initially at KFSH&RC.

The manuscript submitted to the peer reviewed journal, '*The Cleft Palate-Craniofacial Journal*' was accepted for publication.

### 2.7 Project title: Relation Between Breast Feeding and Wilms' Tumor (RAC# 2071004)

**Principal Investigator:** Dr. Saud Alshanafey

**Co-Investigators:** Dr. Ibrahim AlFawaz, and Dr. Tagreed Salman

### Project description

A retrospective study to assess the relationship between breast feeding and wilms' tumor. parents of patients managed at KFSHRC will be contacted by phone and data sheet will be filled. this may bring about a preventive measure if such relation does exist.

### Progress

Data collection phase.

**Project title: Renal Tumors in Infants (outcome study): RAC# 2071 009**

**Principal Investigator:** Dr. Saud Alshanafey

**Co-Investigator:** Dr. Ibrahim Al-Fawaz

### Project description

Retrospective study about renal tumors in infants managed at KFSHRC. the aim is to describe the types

of tumours, its management and outcome.

#### Progress

Data collection phase.

**Project title: Persistent Hyperinsulinemic Hypoglycemia of Infancy (Nesidioblastosis): Pathological stratification (RAC# 2071 010)**

**Principal Investigator:** Dr. Saud Alshanafey  
**Co-Investigator:** Dr. Hindi Al-Hindi

#### Project description

Retrospective review to describe the pathological types of Nesidioblastosis at our population. the distinction between the focal and diffuse forms has major implications on management as shown in recent reports. Also will guide to some genetic studies that could differentiate these patients as well.

#### Progress

Data analysis phase

**Project title: Laparoscopic Versus Open Pancreatectomy For Persistent Hyperinsulinemic Hypoglycemia of Infancy (RAC# 2071 064)**

**Principal Investigator:** Dr. Saud Alshanafey

#### Project description

Comparative study between laparoscopic and open pancreatectomy for nesidioblastosis patients. Our results show that they are comparable and longer follow up is warranted to ascertain that.

#### Progress

Preparing abstract for meetings and manuscript for publication.

**Project title: Laparoscopic Pancreatectomy For Persistent Hyperinsulinemic Hypoglycemia Of Infancy (RAC# 2071 065)**

**Principal Investigator:** Dr. Saud Alshanafey  
**Co-Investigators:** Dr. Saleh Al-nassar and Dr. Zakaria Habib

#### Project description

Review of our experience with laparoscopic pancreatectomy at KFSHRC with special emphasis on technique and outcome. Results showed feasibility and effectivity but longer follow up is needed.

#### Progress

Accepted for presentation as above and manuscript will be sent soon for publication.

**Project title: Effects of Environmental Pollutants Exposure on the Pregnancy Outcome of Women in Al-Kharj Area (BESC# 008\_05, RAC# 2010 006)**

**Principal Investigator:** Dr. Iman Al-Saleh  
**Co-Investigators:** Dr. Gamal El-Din Mohamed, Saleh Al-nassar, Mr. Abdulrahman Abdullah Bin-Muamma, and Dr. Zakaria Habib

#### Progress

Data was successfully cleaned. Preliminary analyses we performed.

Data sets were surrendered for statistical analyses. Projects is completed.

**Project title: TyGER Study (A Multicenter, Open-Label, Randomized Comparative Study of Tigecycline vs Ceftriaxone Sodium Plus Metronidazole for the Treatment of Hospitalized Subjects With Complicated Intra-abdominal Infection, (BESC# 005\_07, RAC# 2061 076)**

**Principal Investigator:** Dr. Abdullah Al Hokail  
**Co-Investigator:** Mr. Abdulrahman Bin-Muammar

#### Project description

Tigecycline is a glycolcycline antibiotic and an analog of the semisynthetic tetracycline, minocycline. The tetracyclines are inhibitors of protein synthesis. However, their utilization is limited because of the emergence of resistance, primarily through an energy-dependent removal of antibiotic via an efflux protein and ribosomal protection. Tigecycline was developed as an intravenous agent to restore therapeutic utility to this tetracycline class by overcoming tetracycline resistance.

Antibiotic resistance presents a significant challenge in treating subjects with complicated intra-abdominal infection (cIAI). The activity of Tigecycline against resistant organisms, as well as significant coverage of both gram-positive and gram-negative bacteria, may provide the clinician with a valuable therapeutic alternative in treating patients with cIAI.

Two phase 3 efficacy, safety, and pharmacokinetic studies of Tigecycline compared to imipenem/cilastatin were conducted in subjects with cIAI at nearly 200 centres worldwide for registration submission. Imipenem/cilastatin was chosen as the comparator for registration purposes. However, other antibiotics are often used to treat cIAI in clinical practice.

This protocol provides the opportunity to compare the efficacy and safety of Tigecycline compared to ceftriaxone sodium plus metronidazole, a commonly used combination, for hospitalized patients with cIAI.

### Progress

The site initiation visit was performed. Patients enrollment has been started.

## FUTURE RESEARCH DIRECTION

In an era of extraordinary advances in scientific knowledge and methods, epidemiology provides essential tools for understanding disease etiology and for identifying effective and efficient approaches to prevention and treatment. The ERU is committed to furthering our understanding of the determinants of population health especially in Saudi Arabia. Staff aim to develop a better understanding of health and prevention of ill health through vigorous research and the development of research methodology.

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## TECHNICAL SUPPORT AND DATA ANALYSIS: COLLABORATIVE RESEARCH

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**Project title: Mitral Balloon Valvotomy – Immediate and Long Term Effect. (RAC # 2001 054)**

**PI:** Mohammed Fawzi, MD  
**BRU I:** Abdelmoneim Eldali  
**BESC #:** 011/1995

### Project description

Mitral balloon valvotomy is an established non-surgical modality for the treatment of severe mitral valve stenosis. Although in children and adolescents with mitral stenosis the immediate and midterm hemodynamic effects of balloon valvotomy have been adequately documented, there is a paucity of data regarding the long-term results of mitral balloon valvotomy in this age group. This project aims to analyze the data of 365 patients with mitral stenosis who were submitted to mitral balloon valvotomy in our institution and to follow up.

The objective is to assess the safety, efficacy and long-term results of mitral balloon valvotomy in children and adolescents in comparison to adults.

### Progress

Data analysis phase. Several publications and presentations resulted from this project.

**Project title: Study, Using a Baboon Model, of the Coagulation Response Patterns to Severe Heat Stress and its Relation to Inflammation and Cell Injury. (RAC #: 2002 067)**

**PI:** Abderrezak Bouchama, MD  
**BRU I:** Abdelmoneim Eldali

### Project description

Heatstroke is associated with massive activation of coagulation leading to microvascular thrombosis in various organs, and death. Knowledge of the molecular mechanisms responsible for this activation of coagulation in heatstroke is important for the development of new modalities of treatment. Using a baboon model of heatstroke, we propose to test the hypothesis that (1) cellular injury and death in heatstroke are the result of disseminated intravascular coagulation initiated

by the expression of tissue factor, and blocking the activation of coagulation either by a tissue factor pathway inhibitor (TFPI) or recombinant activated protein C reduce significantly the coagulopathic and lethal effects of heat. Four baboons are heat stressed to a rectal temperature of 43.5 C (LD100 heat at 48 hours) in a modified neonatal incubator where the environmental temperature is maintained at 47 C. The animals are monitored for vital signs, and the concentrations of coagulation (thrombin-antithrombin complexes, soluble fibrin monomers, D-Dimers, tissue factor) and fibrinolysis components (plasmin-antiplasmin complexes, tissue plasminogen activator and plasminogen activator inhibitor) and inflammatory mediators (TNF, IL-1, IL-6, IL-10) at T=15 minutes during heat stress and T=1, 6, 24, 48 hours during recovery/progression of injury. Four sham-heated baboons will serve as a control group. Survival at 3 days will be compared between each group.

### Progress

Data analysis completed for phase I, II, and III. Several publications and presentations resulted from this project.

**Project title: Gulf Center for Cancer Registration (RC Admin Approved, BESC# 032/2001)**

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

### Project description

The Gulf Center for Cancer Registration (GCCR) was established in 1997. The GCCR works under the jurisdiction of the Executive Office for Ministries of Health Council of GCC countries. The main office is located in the premises of the Research Center, King Faisal Specialist Hospital and Research Center. The GCCR database, population-based incidence data that include information on both benign and malignant primary tumors, is of the largest aggregations in Asia. Compiling data from the six national cancer registries representing the six Gulf countries: Kingdom of Bahrain, Kingdom of Saudi Arabia, State of Kuwait, State of Qatar, Sultanate of Oman and United 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. The National Cancer Registry in each country is responsible for the data

collection at the national level from health facilities that diagnose or treat cancer in that country. Data which include patient's identification, demographics information, site of cancer, histology, stage of the disease, etc. are collected from the patient's medical records based on clinical and histological diagnosis. Collected data will be sent to GCCR main office for ensuring the accuracy of information reported and subsequently for annual data analysis.

### Progress

The population pyramid for each GCC country was produced in SAS® for the GCCR Annual/Cumulative Report 2007.

**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 Naggat M, El Sherif M, Subhani S, Shamy E, Obaid W, Hashim S

### Project description

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a significant cause of morbidity and mortality all over the world. Deep vein thrombosis (DVT) affects primarily the veins of the lower leg and thigh. A thrombus forms in a proximal vein, blocking the flow of blood and often (but not always) causing swelling and inflammation. While deep vein thrombosis is not life threatening, the thrombus can break free and travel to the pulmonary artery or one of its branches and block pulmonary blood flow, leading to pulmonary embolism (PE), the most serious sequela of DVT. The Thromboembolic Disorders Registry of King Faisal Specialist Hospital and Research Center was established in February 2001 as collaboration between Registries Core Facility of Biostatistics, Epidemiology and Scientific Computing Department and King Faisal Internal Medicine Department. All patients presented to the Thromboembolic Service in the section of Internal Medicine are registered. However only those who understand, accept and sign the Informed Consent Forms are included in the registry.

### 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.
- To provide leadership in establishing and maintaining comprehensive TED Registry in collaboration with other National Organization.
- Serve as database for future research.
- 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.
- Enable stratification of patients into different risk groups.

### Progress

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the TEDR Annual/Cumulative Report 2007.

**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

SAS® programs have been written for data analysis and presentation for the CLPR Annual/ Cumulative Report 2007.

**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 and Research Center (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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the Epilepsy Registry Annual/Cumulative Report 2007. Technical support was provided when needed.

**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 determine the types of

neuromuscular diseases found in the population. Moreover, to obtain the 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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the NMDR Annual/Cumulative Report 2007. Technical support is provided when needed.

**Project title: Congenital Heart Disease Registry (RAC# 991 026, BESC# 011/96)**

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

### Project description

Congenital heart defect (CHD) is an inborn anomaly due to unknown causes and is an important cause of infant mortality and morbidity. CHD is defined as a gross structural abnormality of the heart, great vessels or the conduction system that is actually or potentially of functional importance. Studies of the incidence of this disease in populations provide different incidence rates. The congenital heart defects registry of the King Faisal Specialist Hospital and Research Center (KFSH &RC) started in 1998 as 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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the CHDR Annual/Cumulative Report 2007.

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

**Progress**

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the NTDR Annual/Cumulative Report 2007. Technical support is provided when needed.

**Project title: National Diabetes Registry (RC Admin Approved, BESC# 028/2001)**

**Investigators:** Al Rubeaan K, Al Ageel S, Subhani S, Hashim S

**Project description**

Diabetes mellitus (DM) is a major and growing problem in the Kingdom of Saudi Arabia causing prolonged ill health, disability, early death and high health cost. Diabetes being a chronic disease causes chronic complications with high morbidity and mortality rate. To monitor this disease in the Kingdom of Saudi Arabia, a National Diabetes Registry was established in 1996. The DM registry will help in having better knowledge on the geographic distribution, the demographic characteristics and the clustering of DM in families. The DM registry will serve as an easily accessible source for data on Saudi

diabetics. This will encourage researchers to study the problem of DM in the Kingdom. The aggregation, analysis and presentation of information about DM is expected to significantly contribute to the medical understanding, demonstrating trends in management, improving the quality of care for DM patients and supporting planning and development.

**Progress**

Tables, graphs and charts have been produced in SAS® for the purpose of generating the Diabetes Registry Cumulative Report.

**Project title: PCR Assay For Detection And Quantification Of Fungal Infections In Pediatric Patients With Acute Myeloid Leukemia And Myelodysplastic Syndrome. (RAC #: 2021 054)**

**Investigators:** Rajeev K. Sathiapalan, Ibrahim Bin-Hussain, Rong Bu, Asim Belgaumi, Mohammed O. Qutub, Ahmed Al-Ahmari, Faisal Al-Kurdi, Edna Almodovar.

**Project description**

Fungal infections pose a serious challenge to survival of the child with cancer by its life-threatening nature and also compromising definitive treatment of underlying disease. Novel methods for early detection of fungi include polymerase chain reaction (PCR), galactomannan antigenemia, antibody titers and detection of fungal metabolites. Although PCR-based assays targeting unique DNA sequences have been developed for detection and identification of *Candida* and *Aspergillus* species, their application to patients at high risk for invasive mycoses is still in infancy.

A significant number of children with cancer treated at KFSH&RC and KFNC&RC develop fungal infections for unknown reasons. This longitudinal, prospective study aims at early detection of fungi by PCR assay as a surrogate marker of invasive fungal infection in pediatric patients with acute myeloid leukemia and myelodysplastic syndrome treated on acute myeloid leukemia protocol. It is expected to complement the different strategies for reducing the morbidity and mortality from fungal infections.

**Progress**

Data has been collected for 19 patients excluding the

monitoring data of PCR with and without anti-fungal treatment. The database was created in SPSS and preliminary tables were submitted to Dr. Ibrahim Bin-Hussain.

**Project title: The Use Of Chlorhexidine Oral Care For The Prevention Of Ventilator-Associated Pneumonia (VAP). (RAC #: 2021 076)**

**Investigator:** Mohammed Hijazi

#### **Project description**

Despite advances in the field of critical care and infection control, nosocomial pneumonia continues to be a major cause of morbidity and mortality among patients requiring mechanical ventilation and a common source of controversies among their care providers about the best diagnostic, preventive and therapeutic strategies.

Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections in intensive care units. VAP continues to complicate the source of 8 to 28% of patients receiving mechanical ventilation (MV) with mortality rate ranges from 24 to 50% and can reach 76% in some specific settings or when lung infection is caused by high-risk pathogens.

Chlorhexidine is an antiseptic solution that has been used by dentists since 1959 for the control of dental plaque. It is rapidly bactericidal to both gram-positive and gram-negative bacteria and yeast. Chlorhexidine has been studied extensively and shown to decrease aerobic and anaerobic bacteria in the oral cavity from 55 to 97% without any significant changes in bacterial resistance, overgrowth of potentially opportunistic organisms or other adverse changes in the oral microbial ecosystem.

Oral care is performed in all critically ill intubated patients. In our ICU, as in most ICUs, normal saline is used by the nurses for routine oral care. No studies evaluated the use of chlorhexidine-based oral care in the prevention of VAP in medical and non-cardiac surgical critically ill patients. Preventing VAP in this high risk group using a simple and cost effective intervention will lead to fewer days in the ICU, less antibiotic use, less cost and possibly less mortalities.

The objective of the study is to compare oral care using chlorhexidine to the routine oral care on the occurrence of VAP in mechanically ventilated medical and surgical critically ill patients.

#### **Progress/Status**

Data for 346 patients were collected for this study but only 242 cases were included when the exclusion criteria were applied. Final data management activities and statistical analysis were done. This study is completed.

**Project title: Identification Of Environmental And Genetic Factors That Influence Breast Cancer Development And Therapy In Saudi Females. (RAC #: 2031 091 KACST # ARP-2432)**

**Investigators:** Nasser El Kum.

#### **Project description**

The cancer data of the Kingdom of Saudi Arabia show that breast cancer is hitting the largest proportion of the female population of the cancer patients. The high incidence and mortality rates for this type of cancer may be attributed to a number of risk factors which are to be explored for the Saudi population. We found in the Western literature that the factors showing significantly higher risks are: age at presentation; family history of breast cancer; cervix, uterus, or colon; age at first pregnancy after thirty; history of previous breast cancer; early menarche and late menopause; excessive radiation; and obesity.

Because of the lack of any original data on this subject in the Kingdom of Saudi Arabia, a case-control study is planned to be conducted at national level. This research study will describe the risk factors of breast cancer and the relationship among these factors for the Saudi population, thus, giving a better understanding of this disease in this part of the world. On the basis of this research, attempts can be made to lower both the incidence and mortality rates of breast cancer.

#### **Progress**

Data for 1255 patients and 707 controls has been collected and entered in an MS Access database. Data collection is ongoing.

**Project title: Prevalence Of Anemia And The Transfusion Practices In Critically Ill Patients. (RAC #: 2031 018)**

**Investigators:** Khalid Al Maghrabi, Rasheed Al Hubail, Mohammed Hijazi, Nabila Abouchala, Torbjorn Wetterberg, Gamal Mohammed.

### Project description

Anemia is common in critically ill patients. By day 3 of intensive care unit admission, about 95% of the patients have hemoglobin concentration below normal. Blood transfusion and blood conservation are complementary activities that constitute the clinical arena of transfusion medicine. Recent improvement in the safety of the blood supply and the increasing costs associated with transfusion therapies have led to a reevaluation of the clinical practices of blood transfusion and blood conservation.

The transfusion practice in ICU patients is variable and the current transfusion guidelines may not be suitable for critically ill patients. The rate of transfusion in ICU ranges from 4% to 66% with an average transfusion rate of 44%. The rate of transfusion will increase with increasing length of stay in ICU. Hebert PC et al in the TRICC trial demonstrated that using transfusion trigger of 7 gm and maintaining hemoglobin concentration between 7.0-9.0 gm/dl in normovolemic patients is at least as effective as and possibly superior to a liberal transfusion strategy in which a transfusion trigger of 10.0 gm/dl and hemoglobin concentration were maintained at 10.0-12.0 gm/dl were used. With the exception of patients with acute myocardial infarction and unstable angina, using a restrictive strategy of red blood cell transfusion demonstrated a reduction in the total transfusion and decreased the chance for exposure to blood products, which carry a great importance in the presence of donor shortage and variable multiple risks associated with transfusion.

### Progress

Data for 450 patients were collected, but after application of the exclusion criteria, 6 patients were excluded. Data were entered into Excel files which were later converted into SAS. Frequency tables were generated. Statistical analysis will follow.

**Project title: Disseminated Fungal Infections Among Pediatric Patients 0-14 Years Of Age With Hematological Malignancies At KFSH&RC: A Prospective Study. (RAC #: 2041 006)**

**Investigators:** Ali Al-Ahmari, Ibrahim Bin-Hussain, Gamal Mohammed.

### Project description

Invasive fungal infections are more prevalent than ever, presenting an enormous challenge to healthcare professionals. This prevalence is directly related to the growing population of immunocompromised individuals resulting from changes in medical practice such as the use of intensive chemotherapy and immunosuppressive drugs. In the hospital, complicated surgical procedures, widespread use of implanted devices, and the administration of a broad spectrum of antibiotics have dramatically increased the incidence of nosocomial bloodstream infections. Systemic fungal infections are a main cause of morbidity and mortality in patients with hematological malignancies.

### Progress

A 10-page data collection form has been finalized. Data for 108 patients were collected. Data were entered into an MS Access database. Data cleaning and validation are ongoing.

**Project title: Efficacy Of Combination Therapy With Peg-Interferon  $\alpha$ -2a (Pegasys) Plus Ribavirin In The Treatment Of Chronic Hepatitis C: Retrospective Study. (RAC #: 2051 035)**

**Investigators:** Hamad Al Ashgar, Khalid Alsawat, Nasser El Kum, Mohammed Gaseem Khan, Saleim Dahab, Mohammed Al Fadda, Ingvar Kagevi.

### Project description

Infection with hepatitis-C virus (HCV) can result in both acute and chronic hepatitis. Acute infection is usually asymptomatic, rarely leads to hepatic failure but typically leads to chronic infection in 60-80% of cases. Chronic HCV infection is usually slowly progressive; the most common cause of chronic liver disease and the most frequent indication for liver transplantation in some parts of the world. Approximately 20-30% of chronically infected individuals develop cirrhosis over a 20 to 30-year period of time.

In Saudi Arabia the estimated seroprevalence of HCV in community-based study is estimated 1.8% similar result of 1.1% in blood donors. However, surprisingly higher prevalence in hemodialysis patients at 55-68%

in one report. Genotype 4 is predominant in the Middle East and Africa.

Given data from previous studies regarding treatment of chronic HCV infection and the presence of little information in the literature with regards to genotype 4 treatment, we plan to study the experiences in our hospital in the treatment of chronic HCV. It will also include demographic and virology data for this infection.

With the introduction of the current standard therapy for chronic HCV using pegylated interferon combined with Ribavirin, we will evaluate the response rate of patients with chronic HCV.

#### Progress

A 3-page data collection form has been finalized. Data collection is ongoing.

**Project title: Fever Of Unknown Origin (FUO): Experience Of A Tertiary Care Center In Saudi Arabia. (RAC #: 2061 009)**

**Investigators:** Mahmoud A. Moawad, Habib Bassil, Mona Elsherif, Mostafa Elnaggar, Jameela Edathodou, Ibtisam Baksh.

#### Project description

Fever of unknown origin (FUO) is defined as a temperature higher than 38.3 degrees centigrade on several occasions and lasting longer than 3 weeks, with diagnosis that remain uncertain after 1 week of investigation in hospital or in outpatient setting. The condition represents a diagnostic challenge and as such constitutes a significant number of referrals to tertiary care centers. Previous studies have described the spectrum of the disease to be mainly secondary to infectious, neoplastic or inflammatory diseases. Between 9% and 30% in different studies end up without diagnosis despite exhaustive workup. The prognosis of these patients was found to be generally good. Occasionally, deep vein thrombosis (DVT) can present as FUO.

Diagnostic workup that starts with confirming the presence of fever in hospital and emphasizing that there is no "gold standard" test that exists for these patients is well described. Suggested minimal diagnostic workup to qualify as FUO include: complete history and physical examination (H&P) including drug history, CBCD, blood film, routine blood chemistry, urinalysis and microscopy,

blood x 3 and urine cultures, ANA, RF, HIV, CMV IgM antibodies, heterophil antibody test (if consistent with mononucleosis-like syndrome), Q-fever serology (if exposure risk factors exists), CXR, hepatitis serology (if liver enzymes elevated). The role of different nuclear medicine studies (e.g. labeled leukocytes, gallium, Indium & Technitium scans) was emphasized in these patients, especially in ruling-out inflammatory conditions. In one study, immunoscintigraphy with monoclonal antibody 99mTc-BW/250/183 sensitivity in detecting pyogenic foci was 73% and specificity was 97%, positive and negative predictive values were 93% and 87%, respectively.

With the exception of one study from Turkey, no local information is available about FUO in the Middle East. Reporting our experience should fill some of this literature gap and might be of help to our colleagues when they are faced with a patient with FUO.

#### Progress

A 5-page data collection form has been finalized. Data collection is ongoing.

**Project title: Signaling Pathways Involved In Heatstroke Pathogenesis: Role Of Toll-Like Receptor-4 (TLR-4). (RAC #: 2060 013)**

**Investigators:** Mohammed Dehbi, Taher Uz-Zaman, Abderrezak Bouchama, Mohammed Dehbi, Engin Baturcam, Steve Bobis, Moahamed Hassan, Sahar Salem, Ludivina Apilado, Abdelmoneim Eldali and Wilhelmina Ventura.

#### Project description

In this project, we will be focusing on the molecular mechanisms governing the inflammatory, tissue injury and death responses associated with heatstroke using a mouse model. Our initial work is primarily emphasized on the role of TLR-4, a key component involved in various inflammatory responses such as sepsis, shock, burn, trauma, tissue injury and microbial infection, particularly to specific microbial components such as the endotoxin lipopolysaccharide (LPS). Our working hypothesis was based on the observation that heatstroke was associated with a release in the circulation of LPS. In addition, blocking the effects of LPS by administration of anti-lipopolysaccharide agent was shown to improve animal survival from heatstroke effects. These observations prompt us to raise the question as to whether LPS

triggers or potentiates the inflammatory response observed in heatstroke cases. In an attempt to dissect this relationship, we took advantage of the availability of LPS-resistant C3H/HeJ mice, an inbred strain that resists the LPS effects due to a mutation in TLR-4. The wild type strain C3H/HeOuj is used as control.

For each strain, animals were randomly divided into 2 groups: sham-heated group, heatstroke group. Blood and tissue samples will be collected at the onset of heatstroke and at various time points during the recovery period. Expression profiling of a panel of pro-inflammatory and anti-inflammatory mediators will be monitored. Survival rate will be established.

#### **Progress**

A 2-page data collection form has been finalized. Except for the experimental data items, study data has been collected for 141 patients. Of these, 129 are included in the study while 12 were dropped due various reasons, i.e. low body temperature, underweight, died, etc. Data were entered into an SPSS database. Data collection is ongoing.

**Project title: Neuropsychology Study (RAC #: 2061 080)**

**Investigators:** Ahmed M Hassan.

#### **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 of which are MRI, PET, EEG, and Neuropsychological Evaluation. Agreement among those 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**

An SQL database has been created by BESC for this study. The principal investigator himself enters the data into the database. Presently, there are 222 cases in the database. Data has been converted into SAS and SPSS for the PI to do preliminary analysis.

## Research Unit

# REGISTRIES CORE FACILITY

A registry is only attempted when resources are present to support it. Registries working under the umbrella of Registries Core Facility (RCF), Biostatistics, Epidemiology, and Scientific Computing Department (BESC) are on-going research projects with the status of "Active" since their inception. BESC has gained extensive experience in disease registration through its support to several hospital-based, regional and national registries. The BESC department has the expertise to design, develop, and to maintain registry databases as well as proper utilization of collected health data that are usually produced in the form of annual reports and presented in scientific meetings locally and internationally.

Currently RCF is administering several hospital based, regional and national registries. RCF is providing technical and user support to web-based Pan Arab Liver Transplantation Registry, Saudi National Diabetes Registry and several other research projects. Throughout the year 2007, registries staff had been involved in the routine assigned activities of data acquisition (new and follow up cases from clinics, wards, medical records, mainframes), data coding (diagnosis and treatment), data validation and data auditing. Data recorded and reported from individual registries was tabulated and presented as cumulative and/or annual reports. Additionally, the registries staff had been involved in educational activities like (in-house courses, presentations, conferences) as well.

Several data requests for the spin-off projects, after necessary documentation, were furnished to researchers from various registries. Registries annual/cumulative reports were posted on the RCF web-site for year 2006. Several presentations on the research projects were made along with co-authorships on research papers. New collaborations with regional and national hospitals were initiated and activated. Awards winning and recognitions on presented work for the registries on Pan Arab and International levels.

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### **Head:**

**Shazia Naz Subhani**

### **Members:**

Abeer Al-Firm  
 Ahsan Yaseen  
 Ehsan El-Shamy  
 Najah Aftab Siddiqui  
 Nadia Dessouki  
 Lina Barhoush  
 Nada Bawyan  
 Hala Khalil  
 Hanaa Abdulghany  
 Hala Al Assiry  
 Farah Al Meghfy  
 \* Ebthisam Al-Jarba  
 \* Mona Hagos  
 \* Al Gawhara Al Masry

Borrowed Help for the Registries

## CURRENT RESEARCH PROJECTS

**Project title: Congenital Heart Defects Registry (CHDR)**  
**RAC#: 99 1026**

**Investigators:** Dr. Zohair Halees, Dr. Mansour Al Jufan, Dr. Futwan Al Mohanna, Dr. Mohamad Shoukri, Dr. Ahmad Omrani, Ms. Shazia Naz Subhani, Dr. Nadia Dessouky

### Project description

The Congenital Heart Defects Registry (CHDR) of the King Faisal Specialist Hospital and Research Centre (KFSH &RC) was established in 1998 as collaboration between the Department of Biostatistics, Epidemiology and Scientific Computing and the King Faisal Heart Institute. All patients presenting to the hospital with congenital heart disease are registered. Congenital Heart Defects registry is actively collaborating with Prince Sultan Cardiac Centre, Riyadh since year 2003 in terms of remote data acquisition and patient data registration.

### Progress

- Data audited prior to cumulative report data tabulation.
- Cumulative report for KFSH&RC and PSCC were prepared and submitted.
- New version of the web-based software (.NET platform) for the registry was tested and implemented.
- Collaboration with PSCC had been progressive
- Meetings for possible collaborations with King Khalid University Hospital and King Fahad Medical City.
- Statistics for all year cases as of December 31, 2007 is:

Collaborating Hospitals	New cases	Follow up cases	Diagnosis coding	Treatment coding
King Faisal Specialist Hospital & RC	11515	24165	11154	8304
Prince Sultan Cardiac Centre	3522	3533	2697	2388

- Statistics for year 2007 is:

Collaborating Hospitals	New cases	Follow up cases	Diagnosis coding	Treatment coding
King Faisal Specialist Hospital & RC	880	222	580	565
Prince Sultan Cardiac Centre	572	61	912	109

- Disease coder from King Faisal Specialist Hospital & Research Centre is visiting Prince Sultan Cardiac Centre twice a week to complete the backlog of disease coding from year 2003.

### Future Directions

Collaboration with King Fahad Medical City and King Khalid University Hospital, Riyadh.

### Publications

Multi-Institutional Cumulative Report (1998 – 2006).

**Project title: Neural Tube Defects Registry (NTDR)**  
**RAC#: 99 1029E**

**Investigators:** Dr. Essam Al Shail, Dr. Mohammad Al Abdulaaly, Dr. Zayed Al Zayed, Dr. Mohamad Shoukri, Dr. Hoda Kattan, Dr. Wesam Kurdi, Dr. Nadia Sakati, Ms. Shazia Naz Subhani, Ms. Ihsan Yassen

### 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; Disable Children Hospital and Riyadh Medical Complex, Riyadh.

**Progress**

- Data audited prior to annual report data tabulation.
- On-going collaboration with Disabled Children Association.
- Riyadh Medical Centre (RMC), Shemaisy Hospital, has signed a memorandum of agreement with KFSH&RC for collaboration with active data acquisition and entry.
- Collaborative efforts started with King Faisal Specialist Hospital, Jeddah.
- Statistics for all year as of December 31, 2007 is:

	New cases	Follow up
Collaborating Hospitals	523	135

- Statistics for year 2007 is:

	New cases	Follow up
Collaborating Hospitals	40	37

**Future Directions**

On-going collaborations with Disable Children Association and Riyadh Medical Complex. Initiating new collaborations.

**Publications**

Sixth Annual Report with Registrations from October 01, 2000 till December 31, 2006.

**Project title: Epilepsy Registry RAC #: 2011-059**

**Investigators:** Dr. Abdul Aziz Al-Semari, Dr. Donald McLean, Dr. Suad Al-Yamani, Dr. David McDonald, Dr. Z.Patay, Dr. A. Rifaii, Ms. Shazia Naz Subhani, Ms. Najah Aftab Siddiqui

**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**

Completed Data Requests for Publications in year 2007

- Data requested completed in May 2007 for Dr. Ahmed Hassan, senior Neuro-psychologist for his project "A Study to examine the concordance between the neuropsychological data and the EEG, PET and MRI findings in the pre-surgery evaluation of candidates for epilepsy surgery curative intervention" RAC # 2061080.
- Data request of Dr. Hamoud Al Dahash, Neurosurgeon is in process for his research study approved by ORA RAC # 2071042 (PI: Dr. A Al Semari, Dr. Kanaan, Dr. E Shail, Dr. H Dahash).

Completed Data Requests for Presentations & Pilot Studies in year 2007

- Data furnished to Dr. Aziza Chedrawi, consultant neurologist, in June 2007 for her pilot study.
  - Data request of Dr. Hesham Al Dhalaan, consultant neurologist, completed in June 2007 for his pilot study.
  - Dr. Mohammed Dosari has requested data for the Epilepsy Registry workshop and the data has been given to him in June 2007.
  - Data request of Dr. Jamal Ghosheh was completed in June 2007 for his pilot study. He left the hospital shortly after that.
  - Data request of Dr. Suad Al Yamani, consultant neurologist, in process for epilepsy registry workshop.
  - Data request of Dr. Ibrahim Al Thubaiti, Neurosurgeon, in process for epilepsy registry workshop and his pilot study.
  - Data request of Dr. Salah Al Baz, associate neurologist, in process for epilepsy registry workshop.
- Data audited prior to cumulative report data tabulation.
  - Multi-institutional meetings and trainings of multi-institutional users on the registry software.
  - Statistics for all year as of December 31, 2007 is:

	New cases	Diagnosis	Surgery
*Collaborating Hospitals	2629	2333	306

- Statistics for year 2007 is:

	New cases	Diagnosis	Surgery
*Collaborating Hospitals	825	571	20

\* King Faisal Specialist Hospital & Research Centre, Riyadh, King Faisal Specialist Hospital, Jeddah

King Fahad National Guard Hospital, Riyadh Military Hospital

Future Directions

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

Publications

Epilepsy Registry Cumulative Report (2004 - 2005)

**Project title: Cleft Lip / Palate and Craniofacial Anomalies Registry (CLCPR) RAC#: 991-030**

**Investigators:** Dr. Aziza Al Johar, Dr. Essam Al-Shail, Dr. Abdulaziz Al Rubaiya, Kandasamy Ravichandran, Ms. Shazia Naz Subhani, Ms. Ebthisam Al Jarba

Project description

Clefts of the Lip and Palate (CLP) 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.

Over the past couple of years the registry underwent major software modifications to include the Craniofacial Anomalies along with the usual Cleft Lip and Palate patients' registration. The first annual report (Cumulative from 1999 till 2005) is in process of revision and finalization.

Progress

Annual report published after data validation and auditing.

- Paper titled "Prevalence Of Cleft Lip And Palate In Hospital Based Population In Saudi Arabia: Retrospective Study." has been submitted to "The Cleft Palate-Craniofacial Journal" Pittsburgh, US.
- Statistics for all year as of December 31, 2007 is:

	New cases	Treatment Coding
KFSHRC	1088	3308

- Statistics for year 2007 is:

	New cases	Diagnosis Coding	Treatment Coding
KFSHRC	103	99	109

### Future Directions

Collaborations.

### Publications

- Cleft Lip/Palate and Craniofacial Anomalies Registry Annual Report (2006).
- Accepted for Publication paper on Cleft Lip and Cleft palate in King Faisal Specialist Hospital and Research Centre. In American Cleft Palate-Craniofacial Association.

**Project title: Thromboembolic Disorders Registry (TEDR)**  
**RAC#: 2001045**

**Investigators:** Dr. Habib Bassil, Dr. Jalal Saour, Dr. Layla Mammo, Dr. Mohamad Shoukri, Dr. Mansour Aba Al Khail, Dr. Mustafa El Naggat, Dr. Mona. El Sherif, Ms. Shazia Naz Subhani, Ms. Ehsan El-Shamy

### 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 KFSH&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.
- Statistics for all year as of December 31, 2007 is:

	New cases	Follow up cases
KFSHRC	2402	3063

- Statistics for year 2007 is:

	New cases	Follow up cases
KFSHRC	280	66

### Future directions

Collaborations.

### Publications

Thromboembolic Disorders Registry Cumulative Report (2001 - 2006)

**Project title: Neuromuscular Disease Registry (NMDR)**  
**RAC#: 99 1029E**

**Investigators:** Dr. Saeed Bohlega, Dr. Bent Stigsby, Dr. Hisham Al-Dhalan, Ms. Shazia Naz Subhani, Ms. Ahsan Yassen

### 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

- Data audited prior to cumulative report data tabulation.
- Hospital level collaboration started in terms of new and treatment cases reporting on NMD.
- Statistics for all year as of December 31, 2007 is:

	New cases	Diagnosis Coding	Treatment Cases
KFSHRC	1316	1316	1776

- Statistics for year 2007 is:

	New cases	Diagnosis Coding	Treatment Cases
KFSHRC	374	374	429

### Future directions:

Collaborations.

### Publications

Neuromuscular Diseases Registry, 2006 Annual Report.

**Project title: National Diabetes Registry (Research Centre administration approved)**

**Investigators: Dr.Khalid Rubean, Dr. Mohamad Shoukri, Ms. Shazia Naz Subhani, Mr. Saleh Al-Ageel.**

### Project description

Diabetes mellitus is a major and growing problem in the

Kingdom of Saudi Arabia causing prolonged ill-health, disability, early death and high health cost. Diabetes being a chronic disease causes chronic complications with high morbidity and mortality rate. To monitor this disease in the Kingdom of Saudi Arabia, a Saudi Diabetes Registry (SDR) was established in 1996. The SDR main office is located at the Diabetes Center, King Abdulaziz University Hospital, King Saud University. The registry committee consists of members coming from King Saud University, King Faisal Specialist Hospital and Prince Salman Bin Abdulaziz Hospital. The plan is to gradually include hospitals and to require them to file a Diabetes Registry form for every patient where diabetes mellitus have been diagnosed.

As a collaborative contribution from King Faisal Specialist Hospital, a web-based software with a centralized source of data was designed in-house in the BESC department which is activated since the year 2000, registering patients from various hospitals (currently 18 hospitals) from all over Riyadh region.

### Progress

- During the year 2007, three more hospitals joined the registry. Currently there are 20 participating hospitals registering patients using the web-based on-line software.
- As of December 31, 2007 over 41,000 patients registered in the centralized database.
- Several registry presentations were provided to doctors in Ministry of Health and King Abdul Aziz University Hospital.
- Lectures on various diabetes related technical topics were given in the "Diabetes Educators Courses"
- Usage of Geographical Information System enhanced and more maps added to the GIS query engine of the registry.

### Future directions

National Level Collaborations.

### Publications

Various spin off research papers and abstracts.

**Project title: WCST-64 (A Study for Arabic Speaking Individuals) RAC#: 2041048**

**Investigators: Dr. Ahmed Hassan, Najah Aftab Siddiqui**

### Project description

The Wisconsin Card Sorting Test-64 (WCST-64), a shortened version of the WCST-64, and the Word Fluency Test (WFT) are known neuropsychological tools for assessing frontal lobe functioning. In this study, 100 Arabic-speaking male and female normal adults, 20 male and female adult patients with chronic schizophrenia, and 80 male and female adult patients with various focal brain lesions, are evaluated with the WCST-64 and the WFT. The study proposes that the WCST-64 can differentiate adult patients with focal frontal lobe lesions from both normal adult individuals and patients with non-frontal lesions. The aims and objectives of this study are:

1. To obtain local WCST-64 normative data for Arabic-speaking normal individuals (denoted Control Sample).
2. To empirically validate the WCST-64 in clinical samples comprising Arabic-speaking patients with a specific brain dysfunction or a diagnosis of schizophrenia (denoted Clinical Samples).

### Progress

This project started in the 1<sup>st</sup> Quarter of 2005 by Dr. Ahmed Hassan from the Department of Neurosciences. The collaboration with the Department of Biostatistics, Epidemiology and Scientific Computing began by the end of 2<sup>nd</sup> Quarter of 2005. Till the end of the year 2007, some cases fulfilling the criteria were identified and almost 40 cases have been completed.

### Future directions

Completion of the study.

**Project title: Maternal Obesity And Neonatal Congenital Cardiovascular Defects RAC#: 205 1046**

**Investigators:** Ms. Hala Khalil, Dr. Ahmed Saleh, Dr. Futwan Al-Mohanna, Ms. Shazia Naz Subhani

### Project description

Congenital cardiovascular defects (CHDs) are among the most common birth defects. During cardiogenesis various genetic and non-genetic factors can result in developing CHDs. Whether this birth defect is associated with obesity only or other factors was poorly studied. We

undertook this study to compare CHDs in the offspring of non-diabetic overweight, obese women with average weighted women. We reviewed a total of 11, 079 deliveries from 1998-2005. A total of 214 infants who had isolated CHDs diagnosed and treated at our center were matched with 214 normal infants who delivered during the same study period. We excluded all neonates with chromosomal anomalies and mothers with pre-exciting or gestational diabetes, epilepsy, exposed to known teratogens including viral infection. Comparisons were conducted between three groups of women based on their body mass index (BMI) (n = 428). Group 1: average weighted women (control); BMI = 19-25 kg/m<sup>2</sup> (n = 141 women), Group 2: obese women; BMI = 30-34.99 kg/m<sup>2</sup> (n = 228 women) and Group 3: morbidly obese women; BMI ≥ 35 kg/m<sup>2</sup> (n = 59 women). Our results shows that there were no significant differences among the three groups of term and preterm deliveries, periconceptional multivitamin use, current maternal cardiac disease nor family history of cardiac disease. There were strong association between CHDs and previous affected baby with cardiac disease and preterm infants of < 37 weeks gestation (adjusted OR = 3.6, 95% CI: 1.6-8.3 and adjusted OR = 2.3, 95% CI: 1.4-3.9 respectively). We found that no association was found between maternal weight and isolated cardiovascular defects in the offspring.

### Progress

The project has been completed, and a poster has been presented at 'The 5<sup>th</sup> International Medical Congress of National Research Centre, Cairo, Egypt' Dec 2006.

### Publications

Manuscript submitted for publication.

**Project title: Mortality And Causes Of Death In Pediatric Patients With Congenital Heart Defects In A Tertiary Center In Saudi Arabia. RAC# 2071 029**

**Investigators:** Hala S. Khalil, MSc, Ahmed M. Saleh, MD, Futwan Al-Mohanna, PhD, Al-Halees Z, MD, Al-Joufan M, MD, Al-Omrani A, MD and Shazia N. Subhani, MSc

### Project description

Congenital heart defects are the most common serious birth defects that contribute substantially to mortality during early childhood. Medical and surgical treatments

have documented a decrease in mortality rate from heart defects. The purpose of this study is to evaluate the causes of death and survival rate between two cohorts of patients with congenital heart malformations at different ages. A total of 330 pediatric patients aged < 18 years with CHDs who died during the study period 1985 – 2005 will be reviewed. The patients will be divided into two cohort groups; Group 1 patients born and operated on in 1985-1995 and Group 2 patients born and operated on in 1996-2005. Detailed information on how the diagnosis was confirmed, timing of diagnosis whether it was antenatal, immediate postnatal or later, type of cardiovascular defects, associated chromosomal abnormality, medical and extra cardiac malformations and the therapeutic intervention provided (medical, surgical or combination of both) will be collected and analyzed.

#### **Progress**

Data is in the process of being extracted from patients' medical charts.

**Project title: Survey Of Dietary Habits In The Saudi Population. BESC#: 009 2006**

**Investigators:** Dr. Kate S Collison, Dr. Yasmin Al-Twajiri, Dr. Mohamad Shoukri, Ms. Shazia Naz Subhani, Dr. Ali Al-Zahrani

#### **Project description**

In this study, intelligent questions have been asked about the types of foods consumed in light of previous research, to get a clear idea as to dietary patterns amongst the 3 age groups. Dietary patterns have been compared to BMI and Waist-To-Hip ratio measurements. Participants have received a short explanation as to how their involvement will benefit the Saudi population as a whole once the study has been completed. A brief consent form was completed. Data was acquired in an un-biased and non-judgmental way, and upon completion of each survey, participants were offered standard KFSH&RC dietary information leaflets with the aim of improving health awareness.

#### **Progress**

- User training on the web-based software provided to the identified personal.
- Extension of the search engine and analysis module within the web application.
- Over 7,420 data collected and entered by the trained personal into the web-based database.

#### **Future directions**

Data Analysis and Reporting by Statisticians and PI.

## TECHNICAL SUPPORT AND DATA ANALYSIS: COLLABORATIVE RESEARCH

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**Project title: Mitral Balloon Valvotomy – Immediate and Long Term Effect.** (RAC # 2001 054)

**PI: Mohammed Fawzi, MD**  
**BRU I: Abdelmoneim Eldali**  
**BESC #: 011/1995**

### Description

Mitral balloon valvotomy is an established non-surgical modality for the treatment of severe mitral valve stenosis. Although in children and adolescents with mitral stenosis the immediate and midterm hemodynamic effects of balloon valvotomy have been adequately documented, there is a paucity of data regarding the long-term results of mitral balloon valvotomy in this age group. This project aims to analyze the data of 365 patients with mitral stenosis who were submitted to mitral balloon valvotomy in our institution and to follow up.

The objective is to assess the safety, efficacy and long-term results of mitral balloon valvotomy in children and adolescents in comparison to adults.

### Progress

Data analysis phase. Several publications and presentations resulted from this project.

**Project title: Study, Using a Baboon Model, of the Coagulation Response Patterns to Severe Heat Stress and its Relation to Inflammation and Cell Injury.** (RAC #: 2002 067)

**PI: Abderrezak Bouchama, MD**  
**BRU I: Abdelmoneim Eldali**

### Description

Heatstroke is associated with massive activation of coagulation leading to microvascular thrombosis in various organs, and death. Knowledge of the molecular mechanisms responsible for this activation of coagulation in heatstroke is important for the development of new modalities of treatment. Using a baboon model of heatstroke, we propose to test the hypothesis that (1) cellular injury and death in heatstroke are the result

of disseminated intravascular coagulation initiated by the expression of tissue factor, and (2) that blocking the activation of coagulation either by a tissue factor pathway inhibitor (TFPI) or recombinant activated protein C reduce significantly the coagulopathic and lethal effects of heat. Four baboons are heat stressed to a rectal temperature of 43.5°C (LD100 heat at 48 hours) in a modified neonatal incubator where the environmental temperature is maintained at 47°C. The animals are monitored for vital signs, and the concentrations of coagulation (thrombin-antithrombin complexes, soluble fibrin monomers, D-Dimers, tissue factor) and fibrinolysis components (plasmin-antiplasmin complexes, tissue plasminogen activator and plasminogen activator inhibitor) and inflammatory mediators (TNF, IL-1, IL-6, IL-10) at T=15 minutes during heat stress and T=1, 6, 24, 48 hours during recovery/progression of injury. Four sham-heated baboons will serve as a control group. Survival at 3 days will be compared between each group.

### Progress

Data analysis completed for phase I, II, and III. Several publications and presentations resulted from this project.

**Project title: Gulf Center for Cancer Registration (RC Admin Approved, BESC# 032/2001)**

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

### Project Description

The Gulf Center for Cancer Registration (GCCR) was established in 1997. The GCCR works under the jurisdiction of the Executive Office for Ministries of Health Council of GCC countries. The main office is located in the premises of the Research Center, King Faisal Specialist Hospital and Research Center. The GCCR database, population-based incidence data that include information on both benign and malignant primary tumors, is of the largest aggregations in Asia. Compiling data from the six national cancer registries representing the six Gulf countries: Kingdom of Bahrain, Kingdom of Saudi Arabia, State of Kuwait, State of Qatar, Sultanate of Oman and United 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. The National Cancer Registry in each country is responsible for the data collection at the national level from health facilities that diagnose or treat cancer in that country. Data which include patient's identification, demographics information, site of cancer, histology, stage of the disease, etc. are collected from the patient's medical records based on clinical and histological diagnosis. Collected data will be sent to GCCR main office for ensuring the accuracy of information reported and subsequently for annual data analysis.

### Progress

The population pyramid for each GCC country was produced in SAS® for the GCCR Annual/Cumulative Report 2007.

**Project title: Thromboembolic Disorders Registry (RAC# 2001 045, BEC# 004/2001)**

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

### Project Description

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a significant cause of morbidity and mortality all over the world. Deep vein thrombosis (DVT) affects primarily the veins of the lower leg and thigh. A thrombus forms in a proximal vein, blocking the flow of blood and often (but not always) causing swelling and inflammation. While deep vein thrombosis is not life threatening, the thrombus can break free and travel to the pulmonary artery or one of its branches and block pulmonary blood flow, leading to pulmonary embolism (PE), the most serious sequela of DVT. The Thromboembolic Disorders Registry of King Faisal Specialist Hospital and Research Center was established in February 2001 as collaboration between Registries Core Facility of Biostatistics, Epidemiology and Scientific Computing Department and King Faisal Internal Medicine Department. All patients presented to the Thromboembolic Service in the section of Internal Medicine are registered. However only those who understand, accept and sign the Informed Consent Forms are included in the registry.

### 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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the TEDR Annual/Cumulative Report 2007.

**Project title: Cleft Lip/Palate and Craniofacial Anomalies Registry (RAC# 991 030, BEC# 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

SAS® programs have been written for data analysis and presentation for the CLPR Annual/ Cumulative Report 2007.

**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 and Research Center (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**

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the Epilepsy Registry Annual/Cumulative Report 2007. Technical support was provided when needed.

**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 determine the types of neuromuscular diseases found in the population. Moreover, to obtain the 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**

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the NMDR Annual/Cumulative Report 2007. Technical support is provided when needed.

**Project title: Congenital Heart Disease Registry (RAC# 991 026, BESC# 011/96)**

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

**Project Description**

Congenital heart defect (CHD) is an inborn anomaly due to unknown causes and is an important cause of infant mortality and morbidity. CHD is defined as a gross structural abnormality of the heart, great vessels or the conduction system that is actually or potentially of functional importance. Studies of the incidence of this disease in populations provide different incidence rates. The congenital heart defects registry of the King Faisal Specialist Hospital and Research Center (KFSH &RC) started in 1998 as collaboration between the Registries Core Facility of the Biostatistics, Epidemiology and Scientific Computing Department and the King Faisal Heart Institute. All patients presented 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**

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the CHDR Annual/Cumulative Report 2007.

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

#### **Progress**

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the NTDR Annual/Cumulative Report 2007. Technical support is provided when needed.

**Project title: National Diabetes Registry (RC Admin Approved, BESC#028/2001)**

**Investigators:** Al Rubeaan K, Al Ageel S, Subhani S, Hashim S

#### **Project Description**

Diabetes mellitus (DM) is a major and growing problem in the Kingdom of Saudi Arabia causing prolonged ill health,

disability, early death and high health cost. Diabetes being a chronic disease causes chronic complications with high morbidity and mortality rate. To monitor this disease in the Kingdom of Saudi Arabia, a National Diabetes Registry was established in 1996. The DM registry will help in having better knowledge on the geographic distribution, the demographic characteristics and the clustering of DM in families. The DM registry will serve as an easily accessible source for data on Saudi diabetics. This will encourage researchers to study the problem of DM in the Kingdom. The aggregation, analysis and presentation of information about DM is expected to significantly contribute to the medical understanding, demonstrating trends in management, improving the quality of care for DM patients and supporting planning and development.

#### **Progress**

Tables, graphs and charts have been produced in SAS® for the purpose of generating the Diabetes Registry Cumulative Report.

**Project title: PCR Assay For Detection And Quantification Of Fungal Infections In Pediatric Patients With Acute Myeloid Leukemia And Myelodysplastic Syndrome. (RAC #:2021 054)**

**Investigators:** Rajeev K. Sathiapalan, Ibrahim Bin-Hussain, Rong Bu, Asim Belgaumi, Mohammed O. Qutub, Ahmed Al-Ahmari, Faisal Al-Kurdi, Edna Almodovar.

#### **Project description**

Fungal infections pose a serious challenge to survival of the child with cancer by its life-threatening nature and also compromising definitive treatment of underlying disease. Novel methods for early detection of fungi include polymerase chain reaction (PCR), galactomannan antigenemia, antibody titers and detection of fungal metabolites. Although PCR-based assays targeting unique DNA sequences have been developed for detection and identification of *Candida* and *Aspergillus* species, their application to patients at high risk for invasive mycoses is still in infancy.

A significant number of children with cancer treated at KFSH&RC and KFNCC&RC develop fungal infections for unknown reasons. This longitudinal, prospective study aims at early detection of fungi by PCR assay as a surrogate marker of invasive fungal infection in pediatric

patients with acute myeloid leukemia and myelodysplastic syndrome treated on acute myeloid leukemia protocol. It is expected to complement the different strategies for reducing the morbidity and mortality from fungal infections.

### Progress

Data has been collected for 19 patients excluding the monitoring data of PCR with and without anti-fungal treatment. The database was created in SPSS and preliminary tables were submitted to Dr. Ibrahim Bin-Hussain.

**Project title: The Use Of Chlorhexidine Oral Care For The Prevention Of Ventilator-Associated Pneumonia. (RAC #: 2021 076)**

**Investigator:** Mohammed Hijazi

### Project description

Despite advances in the field of critical care and infection control, nosocomial pneumonia continues to be a major cause of morbidity and mortality among patients requiring mechanical ventilation and a common source of controversies among their care providers about the best diagnostic, preventive and therapeutic strategies.

Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections in intensive care units. VAP continues to complicate the source of 8 to 28% of patients receiving mechanical ventilation (MV) with mortality rate ranges from 24 to 50% and can reach 76% in some specific settings or when lung infection is caused by high-risk pathogens.

Chlorhexidine is an antiseptic solution that has been used by dentists since 1959 for the control of dental plaque. It is rapidly bactericidal to both gram-positive and gram-negative bacteria and yeast. Chlorhexidine has been studied extensively and shown to decrease aerobic and anaerobic bacteria in the oral cavity from 55 to 97% without any significant changes in bacterial resistance, overgrowth of potentially opportunistic organisms or other adverse changes in the oral microbial ecosystem.

Oral care is performed in all critically ill intubated patients. In our ICU, as in most ICUs, normal saline is used by the nurses for routine oral care. No studies evaluated the

use of chlorhexidine-based oral care in the prevention of VAP in medical and non-cardiac surgical critically ill patients. Preventing VAP in this high risk group using a simple and cost effective intervention will lead to fewer days in the ICU, less antibiotic use, less cost and possibly less mortalities.

The objective of the study is to compare oral care using chlorhexidine to the routine oral care on the occurrence of VAP in mechanically ventilated medical and surgical critically ill patients.

### Progress/Status

Data for 346 patients were collected for this study but only 242 cases were included when the exclusion criteria were applied. Final data management activities and statistical analysis were done. This study is completed.

**Project title: Identification Of Environmental And Genetic Factors That Influence Breast Cancer Development And Therapy In Saudi Females. (RAC #: 2031 091 KACST # ARP-2432)**

**Investigators:** Nasser El Kum.

### Project description

The cancer data of the Kingdom of Saudi Arabia show that breast cancer is hitting the largest proportion of the female population of the cancer patients. The high incidence and mortality rates for this type of cancer may be attributed to a number of risk factors which are to be explored for the Saudi population. We found in the Western literature that the factors showing significantly higher risks are: age at presentation; family history of breast cancer; cervix, uterus, or colon; age at first pregnancy after thirty; history of previous breast cancer; early menarche and late menopause; excessive radiation; and obesity.

Because of the lack of any original data on this subject in the Kingdom of Saudi Arabia, a case-control study is planned to be conducted at national level. This research study will describe the risk factors of breast cancer and the relationship among these factors for the Saudi population, thus, giving a better understanding of this disease in this part of the world. On the basis of this research, attempts can be made to lower both the incidence and mortality rates of breast cancer.

### Progress

Data for 1255 patients and 707 controls has been collected and entered in an MS Access database. Data collection is ongoing.

**Project title: Prevalence Of Anemia And The Transfusion Practices In Critically Ill Patients. (RAC #: 2031 018)**

**Investigators:** Khalid Al Maghrabi, Rasheed Al Hubail, Mohammed Hijazi, Nabila Abouchala, Torbjorn Wetterberg, Gamal Mohammed.

### Project description

Anemia is common in critically ill patients. By day 3 of intensive care unit admission, about 95% of the patients have hemoglobin concentration below normal. Blood transfusion and blood conservation are complementary activities that constitute the clinical arena of transfusion medicine. Recent improvement in the safety of the blood supply and the increasing costs associated with transfusion therapies have led to a reevaluation of the clinical practices of blood transfusion and blood conservation.

The transfusion practice in ICU patients is variable and the current transfusion guidelines may not be suitable for critically ill patients. The rate of transfusion in ICU ranges from 4% to 66% with an average transfusion rate of 44%. The rate of transfusion will increase with increasing length of stay in ICU. Hebert PC et al in the TRICC trial demonstrated that using transfusion trigger of 7 gm and maintaining hemoglobin concentration between 7.0-9.0 gm/dl in normovolemic patients is at least as effective as and possibly superior to a liberal transfusion strategy in which a transfusion trigger of 10.0 gm/dl and hemoglobin concentration were maintained at 10.0-12.0 gm/dl were used. With the exception of patients with acute myocardial infarction and unstable angina, using a restrictive strategy of red blood cell transfusion demonstrated a reduction in the total transfusion and decreased the chance for exposure to blood products, which carry a great importance in the presence of donor shortage and variable multiple risks associated with transfusion.

### Progress

Data for 450 patients were collected, but after application of the exclusion criteria, 6 patients were excluded. Data

were entered into Excel files which were later converted into SAS. Frequency tables were generated. Statistical analysis will follow.

**Project title: Disseminated Fungal Infections Among Pediatric Patients 0-14 Yearsof Age With Hematological Malignancies At KFSH&RC: A Prospective Study. (RAC #: 2041 006)**

**Investigators:** Ali Al-Ahmari, Ibrahim Bin-Hussain, Gamal Mohammed.

### Project description

Invasive fungal infections are more prevalent than ever, presenting an enormous challenge to healthcare professionals. This prevalence is directly related to the growing population of immunocompromised individuals resulting from changes in medical practice such as the use of intensive chemotherapy and immunosuppressive drugs. In the hospital, complicated surgical procedures, widespread use of implanted devices, and the administration of a broad spectrum of antibiotics have dramatically increased the incidence of nosocomial bloodstream infections. Systemic fungal infections are a main cause of morbidity and mortality in patients with hematological malignancies.

### Progress

A 10-page data collection form has been finalized. Data for 108 patients were collected. Data were entered into an MS Access database. Data cleaning and validation are ongoing.

**Project title: Efficacy Of Combination Therapy With PEG Interferon Alfa-2a (Pegasys) Plus Ribavirin In The Treatment Of Chronic Hepatitis C: Retrospective Study. (RAC #: 2051 035)**

**Investigators:** Hamad Al Ashgar, Khalid Alsawat, Nasser El Kum, Mohammed Qaseem Khan, Saleim Dahab, Mohammed Al Fadda, Ingvar Kagevi.

### Project description

Infection with hepatitis-C virus (HCV) can result in both acute and chronic hepatitis. Acute infection is usually asymptomatic, rarely leads to hepatic failure but typically leads to chronic infection in 60-80% of cases. Chronic HCV infection is usually slowly progressive; the most

common cause of chronic liver disease and the most frequent indication for liver transplantation in some parts of the world. Approximately 20-30% of chronically infected individuals develop cirrhosis over a 20 to 30-year period of time.

In Saudi Arabia the estimated seroprevalence of HCV in community-based study is estimated 1.8% similar result of 1.1% in blood donors. However, surprisingly higher prevalence in hemodialysis patients at 55-68% in one report. Genotype 4 is predominant in the Middle East and Africa.

Given data from previous studies regarding treatment of chronic HCV infection and the presence of little information in the literature with regards to genotype 4 treatment, we plan to study the experience in our hospital in the treatment of chronic HCV. It will also include demographic and virology data for this infection.

With the introduction of the current standard therapy for chronic HCV using pegylated interferon combined with Ribavirin, we will evaluate the response rate of patients with chronic HCV.

### Progress

A 3-page data collection form has been finalized. Data collection is ongoing.

**Project title: Fever Of Unknown Origin: Experience Of A Tertiary Care Center In Saudi Arabia. (RAC #: 2061 009)**

**Investigators:** Mahmoud A. Moawad, Habib Bassil, Mona Elsharif, Mostafa Elnaggar, Jameela Edathodou, Ibtisam Baksh

### Project description

Fever of unknown origin (FUO) is defined as a temperature higher than 38.3 degrees centigrade on several occasions and lasting longer than 3 weeks, with diagnosis that remain uncertain after 1 week of investigation in hospital or in outpatient setting. The condition represents a diagnostic challenge and as such constitutes a significant number of referrals to tertiary care centers. Previous studies have described the spectrum of the disease to be mainly secondary to infectious, neoplastic or inflammatory diseases. Between 9% and 30% in different studies end up without diagnosis despite exhaustive workup. The prognosis of these

patients was found to be generally good. Occasionally, deep vein thrombosis (DVT) can present as FUO.

Diagnostic workup that starts with confirming the presence of fever in hospital and emphasizing that there is no "gold standard" test that exists for these patients is well described. Suggested minimal diagnostic workup to qualify as FUO include: complete history and physical examination including drug history, CBCD, blood film, routine blood chemistry, urinalysis and microscopy, blood x 3 and urine cultures, ANA, RF, HIV, CMV IgM antibodies, heterophil antibody test (if consistent with mononucleosis-like syndrome), Q-fever serology (if exposure risk factors exists), CXR, hepatitis serology (if liver enzymes elevated). The role of different nuclear medicine studies (e.g. labeled leukocytes, gallium, Indium & Technitium scans) was emphasized in these patients, especially in ruling-out inflammatory conditions. In one study, immunoscintigraphy with monoclonal antibody<sup>99mTc-BW/250/183</sup> sensitivity in detecting pyogenic foci was 73% and specificity was 97%, positive and negative predictive values were 93% and 87%, respectively.

With the exception of one study from Turkey, no local information is available about FUO in the Middle East. Reporting our experience should fill some of this literature gap and might be of help to our colleagues when they are faced with a patient with FUO.

### Progress

A 5-page data collection form has been finalized. Data collection is ongoing.

**Project title: Signaling Pathways Involved In Heatstroke Pathogenesis: Role Of Toll-Like Receptor-4 (TLR-4). (RAC #: 2060013)**

**Investigators:** Mohammed Dehbi, Taher Uz-Zaman, Abderrezak Bouchama, Mohammed Dehbi, Engin Baturcam, Steve Bobis, Moahamed Hassan, Sahar Salem, Ludivina Apilado, Abdelmoneim Eldali and Wilhelmina Ventura.

### Project description

In this project, we will be focusing on the molecular mechanisms governing the inflammatory, tissue injury and death responses associated with heatstroke using a mouse model. Our initial work is primarily emphasized on the role of TLR-4, a key component involved in various

inflammatory responses such as sepsis, shock, burn, trauma, tissue injury and microbial infection, particularly to specific microbial components such as the endotoxin lipopolysaccharide (LPS). Our working hypothesis was based on the observation that heatstroke was associated with a release in the circulation of LPS. In addition, blocking the effects of LPS by administration of anti-lipopolysaccharide agent was shown to improve animal survival from heatstroke effects. These observations prompt us to raise the question as to whether LPS triggers or potentiates the inflammatory response observed in heatstroke cases. In an attempt to dissect this relationship, we took advantage of the availability of LPS-resistant C3H/HeJ mice, an inbred strain that resists the LPS effects due to a mutation in TLR-4. The wild type strain C3H/HeOuj is used as control.

For each strain, animals were randomly divided into 2 groups: sham-heated group, heatstroke group. Blood and tissue samples will be collected at the onset of heatstroke and at various time points during the recovery period. Expression profiling of a panel of pro-inflammatory and anti-inflammatory mediators will be monitored. Survival rate will be established.

#### **Progress**

A 2-page data collection form has been finalized. Except for the experimental data items, study data has been collected for 141 patients. Of these, 129 are included in the study while 12 were dropped due various reasons, i.e. low body temperature, underweight, died, etc. Data were entered into an SPSS database. Data collection is ongoing.

**Project title: Neuropsychology Study (RAC #: 2061 080)**

**Investigators:** Ahmed M Hassan

#### **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 of which are MRI, PET, EEG, and Neuropsychological Evaluation. Agreement among those 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**

An SQL database has been created by BESC for this study. The principal investigator himself enters the data into the database. Presently, there are 222 cases in the database. Data has been converted into SAS and SPSS for the PI to do preliminary analysis.

## Core Facility

# TECHNICAL DATABASES

*T*echnical Databases Core Facility (TDBCFC) is a unit within the Department of Biostatistics Epidemiology and Scientific Computing (BESC). The mission of the TDBCFC 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.

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**Head:****Saleh Al Ageel****Members:**

Nirmal Sahar

May Al-Husseini

Lyna Al-Fantookh

Hibah Azem

Fahad Al-Enazy

Bushra Siddiqui (on study leave)

## **APPLICATIONS (DEVELOPED/BEING DEVELOPED YEAR 2007)**

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### **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 KFNBCC&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 through 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.

## **APPLICATIONS RE-DEVELOPED (NEW VERSIONS)**

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As the TDBCFC is aiming to transfer the projects developed in ASP to .Net in order to provide more powerful features and better performance applications,

### **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 TDBCFC 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 TDBCFC 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.

### **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 TDBCFC 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 patient's forms, searching for specific data, exporting data and generating charts, and reports.

### **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 TDBCFC 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.

## **APPLICATIONS (MODIFIED DURING YEAR 2007)**

### **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 Cancer Registry**

The National Cancer Registry (NCR) was established to develop an incidence database and gather other epidemiological data on cancer from all regions of Saudi Arabia. Data is currently gathered using a standalone desktop application that has certain shortcomings (e.g. data redundancy, data security, trouble-shooting, etc.). A Web-based application developed by TDBCF to encourage the centralized cancer registry data management across the country. This application is secure and can be accessed through Internet. The application has features to identify and mark the duplicate records. Unlike current application, it provides real-time reporting.

### **National Epilepsy Registry (ASP 3.0 version)**

A Web-based application to register patients with Epilepsy. It is a national registry. It is the first of its kind in the Kingdom, and can be used as a good resource in the treatment and management of the disease. This application provides from data-entry to data export features. Real-time reports/charts facilities were also incorporated.

### **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.

### **Application for Oligonucleotide Synthesis**

King Faisal Specialist Hospital and Research Centre provides processed primers to researchers working in the hospital or out of the hospital. Aragene Laboratory receives requests from and prepares primers for several KFSHRC Researchers and Non-KFSHRC Researcher on daily basis. The web-based application offers requester his/her registration. A user can start on-line ordering once his/her registration request is accepted by the authorized personnel of Aragene Laboratory.

### **Saudi Thrombosis and Familial Thrombophilia Registry**

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

### **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 KFNBCC&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.

### **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.

### **Venous Thrombosis and Familial Thrombophilia Registry**

The web implementation for Venous Thrombosis and Familial Thrombophilia Registry (VTFT) is designed by TDBCF in 2003. The application is designed to be used nation-wide, providing real-time reports, charts, and data export facilities.

### **Neuromuscular Diseases Registry**

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

## **ONGOING APPLICATION (USERS SUPPORT & MAINTENANCE)**

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### **National Genetic and Birth Defects Registry**

Saudi Arabia has an inordinately large number of birth and genetic diseases; particularly autosomal recessive diseases are encountered more frequently than in the west. This probably is due to consanguineous marriages that have been the custom for many years and to a founder effect. No reliable data is available for their prevalence. A web-based registry application was developed to manage valuable related data for public health and genetic disease prevention programs of the Kingdom.

### **National Premarital Screening Web Application**

The National Premarital Screening Application is a cooperative work between the Research Center and The Ministry of Health (MoH) for Hereditary Blood Diseases .A web-based application is developed in order to facilitate the quest to identify couples at risk and to serve as a future central information reserve to provide better understanding and treatment of the disease.

### **New Born Screening Lab Database**

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. Soon this web database will be extended to a National level web based database system.

### **Allergy and Aerobiology Lab Database Application**

Allergy and Aerobiology Lab receives samples to be tested from various organizations and companies. The web-based application makes it easier for the lab to manage samples and their test result by merging the information in a relational database, accessible from the internet. Samples and their results can be added, viewed, and updated through the application.

### **Research Center Annual Statistical Report Application**

The RC Annual Statistical Report Application is aimed at documenting the activities of the Research Center along with budgeting information of each unit on a yearly basis. A quarterly or annual report based on the activities, employees and budget information of units is generated.

### **Gulf Center for Cancer Registration**

The Gulf Center for Cancer Registration (GCCR) was established to create incidence database and gather other epidemiological data on cancer for the Gulf Cooperation Council (GCC) countries. Under the ministerial approval of the GCC Health Ministers, GCCR collates population-based incidences from GCC and other epidemiological data of cancer.

### **GCC Drug-Abuse Application**

This is a joint project between different collaborating hospitals and King Faisal Specialist Hospital & Research Centre. The users of the GCC countries have designed this project in English as well as in Arabic versions for data entry purposes.

### **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.

#### **Research Center Inventory Management System**

The Research Center Inventory Management System is established to help users to monitor, control and follow up their unit's inventory. The user can add, and edit items in their inventory and also issue several reports on the inventory items

#### **Search Engine Database for Interferon and Cytokine Research Unit**

The web implementation of ARE Database Search Engine has been redesigned with improvements in the speed and appearance. This search engine is one of its kind in all the GCC countries. The application allows the users to perform a search on ARE Database based on criteria like Gene Symbol, Unigene ID, Unigene Definition, Locus, Human Mouse, Refreq ID, Refreq Definition, ARE Cluster Group.

### **USERS' TRAINING**

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TDBCF Section is committed to provide users training sessions at the completion of each application. This year TDBCF has provided one training sessions for users of the National Premarital Screening Application (NPSA).

### **PROFESSIONAL TRAINING**

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#### **TDBCF Trainees**

A new TDBCF staff member, who joined during the year 2007, has given complete training about the technologies being used by the existing staff members.

#### **TDBCF DEMO's**

A demonstration of National Premarital Screening Web application, that was developed with the collaboration of

Ministry of Health (MoH) and being maintained for last 3 years, was given in a workshop organized by MoH during 2007.

### **TECHNICAL SUPPORT AND DATA ANALYSIS: COLLABORATIVE RESEARCH**

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**Project title: Mitral Balloon Valvotomy – Immediate and Long Term Effect. (RAC # 2001 054)**

**PI:** Mohammed Fawzi, MD

**BRU I:** Abdelmoneim Eldali

**BESC #:** O11/1995

#### **Project description**

Mitral balloon valvotomy is an established non-surgical modality for the treatment of severe mitral valve stenosis. Although in children and adolescents with mitral stenosis the immediate and midterm hemodynamic effects of balloon valvotomy have been adequately documented, there is a paucity of data regarding the long-term results of mitral balloon valvotomy in this age group. This project aims to analyze the data of 365 patients with mitral stenosis who were submitted to mitral balloon valvotomy in our institution and to follow up.

The objective is to assess the safety, efficacy and long-term results of mitral balloon valvotomy in children and adolescents in comparison to adults.

#### **Progress**

Data analysis phase. Several publications and presentations resulted from this project.

**Project title: Study, Using a Baboon Model, of the Coagulation Response Patterns to Severe Heat Stress and its Relation to Inflammation and Cell Injury. (RAC #: 2002 067)**

**PI:** Abderrezak Bouchama, MD

**BRU I:** Abdelmoneim Eldali

#### **Project description**

Heatstroke is associated with massive activation of coagulation leading to microvascular thrombosis in various organs, and death. Knowledge of the molecular

mechanisms responsible for this activation of coagulation in heatstroke is important for the development of new modalities of treatment. Using a baboon model of heatstroke, we propose to test the hypothesis that (1) cellular injury and death in heatstroke are the result of disseminated intravascular coagulation initiated by the expression of tissue factor, and (2) that blocking the activation of coagulation either by a tissue factor pathway inhibitor (TFPI) or recombinant activated protein C reduce significantly the coagulopathic and lethal effects of heat. Four baboons are heat stressed to a rectal temperature of 43.5 C (LD100 heat at 48 hours) in a modified neonatal incubator where the environmental temperature is maintained at 47 C. The animals are monitored for vital signs, and the concentrations of coagulation (thrombin-antithrombin complexes, soluble fibrin monomers, D-Dimers, tissue factor) and fibrinolysis components (plasmin-antiplasmin complexes, tissue plasminogen activator and plasminogen activator inhibitor) and inflammatory mediators (TNF, IL-1, IL-6, IL-10) at T=15 minutes during heat stress and T=1, 6, 24, 48 hours during recovery/progression of injury. Four sham-heated baboons will serve as a control group. Survival at 3 days will be compared between each group.

### Progress

Data analysis completed for phase I, II, and III. Several publications and presentations resulted from this project.

**Project title: Gulf Center for Cancer Registration (RC Admin Approved, BESC# 032/2001)**

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

### Project description

The Gulf Center for Cancer Registration (GCCR) was established in 1997. The GCCR works under the jurisdiction of the Executive Office for Ministries of Health Council of GCC countries. The main office is located in the premises of the Research Center, King Faisal Specialist Hospital and Research Center. The GCCR database, population-based incidence data that include information on both benign and malignant primary tumors, is of the largest aggregations in Asia. Compiling data from the six national cancer registries representing the six Gulf countries: Kingdom of Bahrain, Kingdom of Saudi Arabia, State of Kuwait, State of Qatar, Sultanate of

Oman and United 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. The National Cancer Registry in each country is responsible for the data collection at the national level from health facilities that diagnose or treat cancer in that country. Data which include patient's identification, demographics information, site of cancer, histology, stage of the disease, etc. are collected from the patient's medical records based on clinical and histological diagnosis. Collected data will be sent to GCCR main office for ensuring the accuracy of information reported and subsequently for annual data analysis.

### Progress

The population pyramid for each GCC country was produced in SAS® for the GCCR Annual/Cumulative Report 2007.

**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

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a significant cause of morbidity and mortality all over the world. Deep vein thrombosis (DVT) affects primarily the veins of the lower leg and thigh. A thrombus forms in a proximal vein, blocking the flow of blood and often (but not always) causing swelling and inflammation. While deep vein thrombosis is not life threatening, the thrombus can break free and travel to the pulmonary artery or one of its branches and block pulmonary blood flow, leading to pulmonary embolism (PE), the most serious sequela of DVT. The Thromboembolic Disorders Registry of King Faisal Specialist Hospital and Research Center was established in February 2001 as collaboration between Registries Core Facility of Biostatistics, Epidemiology and Scientific Computing Department and King Faisal Internal Medicine Department. All patients presented to the Thromboembolic Service in the section of Internal Medicine are registered. However only those who understand, accept and sign the Informed Consent Forms are included in the registry.

### 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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the TEDR Annual/Cumulative Report 2007.

**Project title: Cleft Lip/Palate and Craniofacial Anomalies Registry (RAC# 991 030, BESEC# 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

SAS® programs have been written for data analysis and presentation for the CLPR Annual/ Cumulative Report 2007.

**Project title: Epilepsy Registry (RAC# 2011 059, BESEC# 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 and Research Center (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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the Epilepsy Registry Annual/Cumulative Report 2007. Technical support was provided when needed.

**Project title: Neuromuscular Disease Registry (RAC# 2031 053, BESEC# 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 determine the types of neuromuscular diseases found in the population. Moreover, to obtain the 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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the NMDR Annual/Cumulative Report 2007. Technical support is provided when needed.

**Project title: Congenital Heart Disease Registry (RAC# 991 026, BESC# 011/96)**

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

#### Project description

Congenital heart defect (CHD) is an inborn anomaly due to unknown causes and is an important cause of infant mortality and morbidity. CHD is defined as a gross structural abnormality of the heart, great vessels or the conduction system that is actually or potentially of functional importance. Studies of the incidence of this disease in populations provide different incidence rates. The congenital heart defects registry of the King Faisal Specialist Hospital and Research Center (KFSH &RC) started in 1998 as 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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the CHDR Annual/Cumulative Report 2007.

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

#### Progress

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the NTDR Annual/Cumulative Report 2007. Technical support is provided when needed.

**Project title: National Diabetes Registry (RC Admin Approved, BESC# 028/2001)**

**Investigators:** Al Rubeaan K, Al Ageel S, Subhani S, Hashim S

#### Project description

Diabetes mellitus (DM) is a major and growing problem in the Kingdom of Saudi Arabia causing prolonged ill health,

disability, early death and high health cost. Diabetes being a chronic disease causes chronic complications with high morbidity and mortality rate. To monitor this disease in the Kingdom of Saudi Arabia, a National Diabetes Registry was established in 1996. The DM registry will help in having better knowledge on the geographic distribution, the demographic characteristics and the clustering of DM in families. The DM registry will serve as an easily accessible source for data on Saudi diabetics. This will encourage researchers to study the problem of DM in the Kingdom. The aggregation, analysis and presentation of information about DM is expected to significantly contribute to the medical understanding, demonstrating trends in management, improving the quality of care for DM patients and supporting planning and development.

#### Progress

Tables, graphs and charts have been produced in SAS® for the purpose of generating the Diabetes Registry Cumulative Report.

**Project title: PCR Assay For Detection And Quantification Of Fungal Infections In Pediatric Patients With Acute Myeloid Leukemia And Myelodysplastic Syndrome. (RAC #: 2021 054)**

**Investigators:** Rajeev K. Sathiapalan, Ibrahim Bin-Hussain, Rong Bu, Asim Belgaumi, Mohammed O. Qutub, Ahmed Al-Ahmari, Faisal Al-Kurdi, Edna Almodovar.

#### Project description

Fungal infections pose a serious challenge to survival of the child with cancer by its life-threatening nature and also compromising definitive treatment of underlying disease. Novel methods for early detection of fungi include polymerase chain reaction (PCR), galactomannan antigenemia, antibody titers and detection of fungal metabolites. Although PCR-based assays targeting unique DNA sequences have been developed for detection and identification of *Candida* and *Aspergillus* species, their application to patients at high risk for invasive mycoses is still in infancy.

A significant number of children with cancer treated at KFSH&RC and KFNC&RC develop fungal infections for unknown reasons. This longitudinal, prospective study aims at early detection of fungi by PCR assay as a surrogate marker of invasive fungal infection in pediatric patients with acute myeloid leukemia and myelodysplastic

syndrome treated on acute myeloid leukemia protocol. It is expected to complement the different strategies for reducing the morbidity and mortality from fungal infections.

#### Progress

Data has been collected for 19 patients excluding the monitoring data of PCR with and without anti-fungal treatment. The database was created in SPSS and preliminary tables were submitted to Dr. Ibrahim Bin-Hussain.

**Project title: The Use Of Chlorhexidine Oral Care For The Prevention Of Ventilator-Associated Pneumonia. (RAC #: 2021 076)**

**Investigator:** Mohammed Hijazi

#### Project description

Despite advances in the field of critical care and infection control, nosocomial pneumonia continues to be a major cause of morbidity and mortality among patients requiring mechanical ventilation and a common source of controversies among their care providers about the best diagnostic, preventive and therapeutic strategies.

Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections in intensive care units. VAP continues to complicate the source of 8 to 28% of patients receiving mechanical ventilation (MV) with mortality rate ranges from 24 to 50% and can reach 76% in some specific settings or when lung infection is caused by high-risk pathogens.

Chlorhexidine is an antiseptic solution that has been used by dentists since 1959 for the control of dental plaque. It is rapidly bactericidal to both gram-positive and gram-negative bacteria and yeast. Chlorhexidine has been studied extensively and shown to decrease aerobic and anaerobic bacteria in the oral cavity from 55 to 97% without any significant changes in bacterial resistance, overgrowth of potentially opportunistic organisms or other adverse changes in the oral microbial ecosystem.

Oral care is performed in all critically ill intubated patients. In our ICU, as in most ICUs, normal saline is used by the nurses for routine oral care. No studies evaluated the use of chlorhexidine-based oral care in the prevention of VAP in medical and non-cardiac surgical critically ill patients. Preventing VAP in this high risk group using a

simple and cost effective intervention will lead to fewer days in the ICU, less antibiotic use, less cost and possibly less mortalities.

The objective of the study is to compare oral care using chlorhexidine to the routine oral care on the occurrence of VAP in mechanically ventilated medical and surgical critically ill patients.

### Progress

Data for 346 patients were collected for this study but only 242 cases were included when the exclusion criteria were applied. Final data management activities and statistical analysis were done. This study is completed.

**Project title: Identification Of Environmental And Genetic Factors That Influence Breast Cancer Development And Therapy In Saudi Females. (RAC #: 2031 091 KACST # ARP-2432)**

**Investigators:** Nasser El Kum

### Project description

The cancer data of the Kingdom of Saudi Arabia show that breast cancer is hitting the largest proportion of the female population of the cancer patients. The high incidence and mortality rates for this type of cancer may be attributed to a number of risk factors which are to be explored for the Saudi population. We found in the Western literature that the factors showing significantly higher risks are: age at presentation; family history of breast cancer, cervix, uterus, or colon; age at first pregnancy after thirty; history of previous breast cancer, early menarche and late menopause; excessive radiation; and obesity.

Because of the lack of any original data on this subject in the Kingdom of Saudi Arabia, a case-control study is planned to be conducted at national level. This research study will describe the risk factors of breast cancer and the relationship among these factors for the Saudi population, thus, giving a better understanding of this disease in this part of the world. On the basis of this research, attempts can be made to lower both the incidence and mortality rates of breast cancer.

### Progress

Data for 1255 patients and 707 controls has been

collected and entered in an MS Access database. Data collection is ongoing.

**Project title: Prevalence Of Anemia And The Transfusion Practices In Critically Ill Patients. (RAC #: 2031 018)**

**Investigators:** Khalid Al Maghrabi, Rasheed Al Hubail, Mohammed Hijazi, Nabila Abouchala, Torbjorn Wetterberg, Gamal Mohammed.

### Project description

Anemia is common in critically ill patients. By day 3 of intensive care unit admission, about 95% of the patients have hemoglobin concentration below normal. Blood transfusion and blood conservation are complementary activities that constitute the clinical arena of transfusion medicine. Recent improvement in the safety of the blood supply and the increasing costs associated with transfusion therapies have led to a reevaluation of the clinical practices of blood transfusion and blood conservation.

The transfusion practice in ICU patients is variable and the current transfusion guidelines may not be suitable for critically ill patients. The rate of transfusion in ICU ranges from 4% to 66% with an average transfusion rate of 44%. The rate of transfusion will increase with increasing length of stay in ICU. Hebert PC et al in the TRICC trial demonstrated that using transfusion trigger of 7 gm and maintaining hemoglobin concentration between 7.0-9.0 gm/dl in normovolemic patients is at least as effective as and possibly superior to a liberal transfusion strategy in which a transfusion trigger of 10.0 gm/dl and hemoglobin concentration were maintained at 10.0-12.0 gm/dl were used. With the exception of patients with acute myocardial infarction and unstable angina, using a restrictive strategy of red blood cell transfusion demonstrated a reduction in the total transfusion and decreased the chance for exposure to blood products, which carry a great importance in the presence of donor shortage and variable multiple risks associated with transfusion.

### Progress

Data for 450 patients were collected, but after application of the exclusion criteria, 6 patients were excluded. Data were entered into Excel files which were later converted into SAS. Frequency tables were generated. Statistical analysis will follow.

**Project title: Disseminated Fungal Infections Among Pediatric Patients 0-14 Years Of Age With Hematological Malignancies At KFSH&RC: A prospective study. (RAC #: 2041 006)**

**Investigators:** Ali Al-Ahmari, Ibrahim Bin-Hussain, Gamal Mohammed.

#### **Project description**

Invasive fungal infections are more prevalent than ever, presenting an enormous challenge to healthcare professionals. This prevalence is directly related to the growing population of immunocompromised individuals resulting from changes in medical practice such as the use of intensive chemotherapy and immunosuppressive drugs. In the hospital, complicated surgical procedures, widespread use of implanted devices, and the administration of a broad spectrum of antibiotics have dramatically increased the incidence of nosocomial bloodstream infections. Systemic fungal infections are a main cause of morbidity and mortality in patients with hematological malignancies.

#### **Progress**

A 10-page data collection form has been finalized. Data for 108 patients were collected. Data were entered into an MS Access database. Data cleaning and validation are ongoing.

**Project title: Efficacy of combination therapy with PEG Interferon Alfa-2a (Pegasys) plus Ribavirin in the treatment of chronic hepatitis C: Retrospective study. (RAC #: 2051 035)**

**Investigators:** Hamad Al Ashgar, Khalid Alsawat, Nasser El Kum, Mohammed Qaseem Khan, Saleim Dahab, Mohammed Al Fadda, Ingvar Kagevi.

#### **Project description**

Infection with hepatitis-C virus (HCV) can result in both acute and chronic hepatitis. Acute infection is usually asymptomatic, rarely leads to hepatic failure but typically leads to chronic infection in 60-80% of cases. Chronic HCV infection is usually slowly progressive; the most common cause of chronic liver disease and the most frequent indication for liver transplantation in some parts of the world. Approximately 20-30% of chronically infected individuals develop cirrhosis over a 20 to 30-year period of time.

In Saudi Arabia the estimated seroprevalence of HCV in community-based study is estimated 1.8% similar result of 1.1% in blood donors, however, surprisingly higher prevalence in hemodialysis patients at 55-68% in one report. Genotype 4 is predominant in the Middle East and Africa.

Given data from previous studies regarding treatment of chronic HCV infection and the presence of little information in the literature with regards to genotype 4 treatment, we plan to study the experience in our hospital in the treatment of chronic HCV. It will also include demographic and virology data for this infection.

With the introduction of the current standard therapy for chronic HCV using pegylated interferon combined with Ribavirin, we will evaluate the response rate of patients with chronic HCV.

#### **Progress**

A 3-page data collection form has been finalized. Data collection is ongoing.

**Project title: Fever of unknown origin: Experience of a tertiary care center in Saudi Arabia. (RAC #: 2061 009)**

**Investigators:** Mahmoud A. Moawad, Habib Bassil, Mona Elsherif, Mostafa Elnaggar, Jameela Edathodou, Ibtisam Baksh.

#### **Project description**

Fever of unknown origin (FUO) is defined as a temperature higher than 38.3 degrees centigrade on several occasions and lasting longer than 3 weeks, with diagnosis that remain uncertain after 1 week of investigation in hospital or in outpatient setting. The condition represents a diagnostic challenge and as such constitutes a significant number of referrals to tertiary care centers. Previous studies have described the spectrum of the disease to be mainly secondary to infectious, neoplastic or inflammatory diseases. Between 9% and 30% in different studies end up without diagnosis despite exhaustive workup. The prognosis of these patients was found to be generally good. Occasionally, deep vein thrombosis (DVT) can present as FUO.

Diagnostic workup that starts with confirming the presence of fever in hospital and emphasizing that there

is no "gold standard" test that exists for these patients is well described. Suggested minimal diagnostic workup to qualify as FUD include: complete H&P including drug history, CBCD, blood film, routine blood chemistry, urinalysis and microscopy, blood x 3 and urine cultures, ANA, RF, HIV, CMV IgM antibodies, heterophil antibody test (if consistent with mononucleosis-like syndrome), Q-fever serology (if exposure risk factors exists), CXR, hepatitis serology (if liver enzymes elevated). The role of different nuclear medicine studies (e.g. labeled leukocytes, gallium, Indium & Technitium scans) was emphasized in these patients, especially in ruling-out inflammatory conditions. In one study, immunoscintigraphy with monoclonal antibody 99mTc-BW/250/183 sensitivity in detecting pyogenic foci was 73% and specificity was 97%, positive and negative predictive values were 93% and 87%, respectively.

With the exception of one study from Turkey, no local information is available about FUD in the Middle East. Reporting our experience should fill some of this literature gap and might be of help to our colleagues when they are faced with a patient with FUD.

#### **Progress**

A 5-page data collection form has been finalized. Data collection is ongoing.

**Project title: Signaling Pathways Involved In Heatstroke Pathogenesis: Role Of Toll-Like Receptor-4 (TLR-4). (RAC #: 2060013)**

**Investigators:** Mohammed Dehbi, Taher Uz-Zaman, Abderrezak Bouchama, Mohammed Dehbi, Engin Baturcam, Steve Bobis, Moahamed Hassan, Sahar Salem, Ludivina Apilado, Abdelmoneim Eldali and Wilhelmina Ventura.

#### **Project description**

In this project, we will be focusing on the molecular mechanisms governing the inflammatory, tissue injury and death responses associated with heatstroke using a mouse model. Our initial work is primarily emphasized on the role of TLR-4, a key component involved in various inflammatory responses such as sepsis, shock, burn, trauma, tissue injury and microbial infection, particularly to specific microbial components such as the endotoxin lipopolysaccharide (LPS). Our working hypothesis was based on the observation that heatstroke was associated

with a release in the circulation of LPS. In addition, blocking the effects of LPS by administration of anti-lipopolysaccharide agent was shown to improve animal survival from heatstroke effects. These observations prompt us to raise the question as to whether LPS triggers or potentiates the inflammatory response observed in heatstroke cases. In an attempt to dissect this relationship, we took advantage of the availability of LPS-resistant C3H/HeJ mice, an inbred strain that resists the LPS effects due to a mutation in TLR-4. The wild type strain C3H/HeOJ is used as control.

For each strain, animals were randomly divided into 2 groups: sham-heated group, heatstroke group. Blood and tissue samples will be collected at the onset of heatstroke and at various time points during the recovery period. Expression profiling of a panel of pro-inflammatory and anti-inflammatory mediators will be monitored. Survival rate will be established.

#### **Progress**

A 2-page data collection form has been finalized. Except for the experimental data items, study data has been collected for 141 patients. Of these, 129 are included in the study while 12 were dropped due various reasons, i.e. low body temperature, underweight, died, etc. Data were entered into an SPSS database. Data collection is ongoing.

**Project title: Neuropsychology Study (RAC #: 2061080)**

**Investigators:** Ahmed M Hassan.

#### **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 of which are MRI, PET, EEG, and Neuropsychological Evaluation. Agreement among those 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**

An SQL database has been created by BESC for this study. The principal investigator himself enters the data into the database. Presently, there are 222 cases in the database. Data has been converted into SAS and SPSS for the PI to do preliminary analysis.



## Core Facility

# COMPUTING SERVICES

The Computing Services Core Facility is playing a major role by providing information technology support to the Research Centre which is a projects oriented institution

The Computing Services Core Facility 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 Computing Services Core Facility 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.

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**Head:****Parvez A. Siddiqui****Members:**

Mashnouf Al-Rowaily

Yosef Hussain

Bander AlKhoudairy

Arnie Tayco

Michael Edquiban

## 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. In the year covered, the unit's collective fund of knowledge was enhanced by expertise gained from such courses.

### Courses Attended by CSCF Staff member

Course Name	CSCF staff member
MS SQL 2005 Administration	Mr. Mashnouf Mr. Bander

## 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 2007, CSCF setup new PCs, laptops, workstation, printers, servers and other major computer peripherals. The CSCF was successful in setting up and configuring two new servers with Windows Server 2003 operating software. One of them will replace the existing Web Server (Al-Biruni) and other one will be used as a file server for RC users and lab data.

### Preventative Maintenance

CSCF successfully carried out the preventative maintenance (PM) in the BESC department. The preventative maintenance consists of 31+ tasks that would boost the performance of the machines, stabilize platforms, and increase the productivity and efficiency and will reduce the support costs. These tasks are related but not limited to:

1. Operating systems updates
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 units subsequently delivered to respective department chairman.

### 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 then ADL), 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:

**BMR Administration:** Setup and configured PCs; troubleshoot hardware and software problems.

**BMR Environment Health:** Setup and configured PCs to be used with laboratory instrument.

**BMR DNA Repair and Apoptosis:** Setup, reconfigured laptops and hooked up PCs with instruments. Updated scientific software like CP on CD and Lasergene.

**BMR DNA Sequencing:** Setup and configured PCs and printers.

**BMR Cell Biology:** Setup and reconfigured PCs for the users as well as PCs to read gels with audio/video links; upgraded hardware and software as required.

**BMR Molecular Oncology:** Setup and configured a laptop, upgraded the operating system.

**BMR Pharmacology:** Installed and configured PCs.

**BMR Molecular Virology and Infectious Diseases:** Setup, configured new PCs and also updated old PCs.

**BRP:** Installed, configured and setup PCs; configured network printers. Install scientific software like CP on CD and Lasergene.

**RC Administration:** Setup and configured new PCs and printers for the users, relocated PCs network connections and printers; setup laptop and projector for meetings and presentation. Setup IMAC and XPS Dell systems.

**Department of Cyclotron and Radiopharmaceuticals:** Setup and configured PCs and laptops.

**Department of Biomedical Physics:** Setup, configured, installed, and supported PCs and laptops.

**Department of Comparative Medicine:** Setup, configured, and upgraded PCs to be used in the laboratory. Also setup and configured laptops.

**Department of Genetics:** Setup and configured PCs, laptops and Printers. .

**NLNBS:** Setup and configured new PCs, Printers and Sample Punching machine. PCs were disjoined from NLNBS domain and rejoined to Internal domain due to some network problems.

**KFNCCC&R:** Setup and configured PCs and Printers.

**SDL Project:** Setup and configured PCs. Reconfigured LIMS servers. Setup new SDL server to replace the old Starfruit server.

**Oncology Data Unit Department of Oncology:** Installed software, supported PCs, and backed-up the data.

Following is the summary of the calls per department logged by CSCF during the year 2007

Department	No. of Logged Calls
BESC	398
BMR	319
BRC	36
BRP	81
BMP	130
C&R	51
CCSEE	86
CMD	173
CPPEO	13
Genetics	372
NLNBS	143
ORA	74
RAC-Admin	137
Stem Cell Therapy	82
T&E	23
KFNCCC-Research	70
KFNCCCO Research (ADL)	69
CDU	10
King Faisal Heart Institute	2
Total calls logged	2269
Total calls not logged	836
<b>TOTAL</b>	<b>3105</b>

## **TECHNICAL SUPPORT AND DATA ANALYSIS: COLLABORATIVE RESEARCH**

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**Project title: Mitral Balloon Valvotomy – Immediate and Long Term Effect. (RAC # 2001 054)**

**PI:** Mohammed Fawzi, MD  
**BRU I:** Abdelmoneim Eldali  
**BESC #:** 011/1995

### **Project description**

Mitral balloon valvotomy is an established non-surgical modality for the treatment of severe mitral valve stenosis. Although in children and adolescents with mitral stenosis the immediate and midterm hemodynamic effects of balloon valvotomy have been adequately documented, there is a paucity of data regarding the long-term results of mitral balloon valvotomy in this age group. This project aims to analyze the data of 365 patients with mitral stenosis who were submitted to mitral balloon valvotomy in our institution and to follow up.

The objective is to assess the safety, efficacy and long-term results of mitral balloon valvotomy in children and adolescents in comparison to adults.

### **Progress**

Data analysis phase. Several publications and presentations resulted from this project.

**Project title: Study, Using a Baboon Model, of the Coagulation Response Patterns to Severe Heat Stress and its Relation to Inflammation and Cell Injury. (RAC #: 2002 067)**

**PI:** Abderrezak Bouchama, MD  
**BRU I:** Abdelmoneim Eldali

### **Project description**

Heatstroke is associated with massive activation of coagulation leading to microvascular thrombosis in various organs, and death. Knowledge of the molecular mechanisms responsible for this activation of coagulation in heatstroke is important for the development of new modalities of treatment. Using a baboon model of heatstroke, we propose to test the hypothesis that (1) cellular injury and death in heatstroke are the result of disseminated intravascular coagulation initiated by

the expression of tissue factor, and (2) that blocking the activation of coagulation either by a tissue factor pathway inhibitor (TFPI) or recombinant activated protein C reduce significantly the coagulopathic and lethal effects of heat. Four baboons are heat stressed to a rectal temperature of 43.5 C (LD100 heat at 48 hours) in a modified neonatal incubator where the environmental temperature is maintained at 47 C. The animals are monitored for vital signs, and the concentrations of coagulation (thrombin-antithrombin complexes, soluble fibrin monomers, D-Dimers, tissue factor) and fibrinolysis components (plasmin-antiplasmin complexes, tissue plasminogen activator and plasminogen activator inhibitor) and inflammatory mediators (TNF, IL-1, IL-6, IL-10) at T=15 minutes during heat stress and T=1, 6, 24, 48 hours during recovery/progression of injury. Four sham-heated baboons will serve as a control group. Survival at 3 days will be compared between each group.

### **Progress**

Data analysis completed for phase I, II, and III. Several publications and presentations resulted from this project.

**Project title: Gulf Center for Cancer Registration (RC Admin Approved, BESC# 032/2001)**

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

### **Project description**

The Gulf Center for Cancer Registration (GCCR) was established in 1997. The GCCR works under the jurisdiction of the Executive Office for Ministries of Health Council of GCC countries. The main office is located in the premises of the Research Center, King Faisal Specialist Hospital and Research Center. The GCCR database, population-based incidence data that include information on both benign and malignant primary tumors, is of the largest aggregations in Asia. Compiling data from the six national cancer registries representing the six Gulf countries: Kingdom of Bahrain, Kingdom of Saudi Arabia, State of Kuwait, State of Qatar, Sultanate of Oman and United 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. The National Cancer Registry in each country is responsible for the data

collection at the national level from health facilities that diagnose or treat cancer in that country. Data which include patient's identification, demographics information, site of cancer, histology, stage of the disease, etc. are collected from the patient's medical records based on clinical and histological diagnosis. Collected data will be sent to GCCR main office for ensuring the accuracy of information reported and subsequently for annual data analysis.

### Progress

The population pyramid for each GCC country was produced in SAS® for the GCCR Annual/Cumulative Report 2007.

**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 Naggat M, El Sherif M, Subhani S, Shamy E, Obaid W, Hashim S

### Project description

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a significant cause of morbidity and mortality all over the world. Deep vein thrombosis (DVT) affects primarily the veins of the lower leg and thigh. A thrombus forms in a proximal vein, blocking the flow of blood and often (but not always) causing swelling and inflammation. While deep vein thrombosis is not life threatening, the thrombus can break free and travel to the pulmonary artery or one of its branches and block pulmonary blood flow, leading to pulmonary embolism (PE), the most serious sequela of DVT. The Thromboembolic Disorders Registry of King Faisal Specialist Hospital and Research Center was established in February 2001 as collaboration between Registries Core Facility of Biostatistics, Epidemiology and Scientific Computing Department and King Faisal Internal Medicine Department. All patients presenting to the Thromboembolic Service in the section of Internal Medicine are registered. However only those who understand, accept and sign the Informed Consent Forms are included in the registry. 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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the TEDR Annual/Cumulative Report 2007.

**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

SAS® programs have been written for data analysis and presentation for the CLPR Annual/ Cumulative Report 2007.

**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 and Research Center (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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the Epilepsy Registry Annual/Cumulative Report 2007. Technical support was provided when needed.

**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 determine the types of neuromuscular diseases found in the population. Moreover, to obtain the 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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the NMDR Annual/Cumulative Report 2007. Technical support is provided when needed.

**Project title: Congenital Heart Disease Registry (RAC# 991 026, BESC# 011/96)**

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

#### Project description

Congenital heart defect (CHD) is an inborn anomaly due to unknown causes and is an important cause of infant mortality and morbidity. CHD is defined as a gross structural abnormality of the heart, great vessels or the conduction system that is actually or potentially of functional importance. Studies of the incidence of this disease in populations provide different incidence rates. The congenital heart defects registry of the King Faisal Specialist Hospital and Research Center (KFSH &RC) started in 1998 as 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

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the CHDR Annual/Cumulative Report 2007.

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

#### Progress

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the NTDR Annual/Cumulative Report 2007. Technical support is provided when needed.

**Project title: National Diabetes Registry (RC Admin Approved, BESC# O28/2001)**

**Investigators:** Al Rubeaan K, Al Ageel S, Subhani S, Hashim S

#### Project description

Diabetes mellitus (DM) is a major and growing problem in the Kingdom of Saudi Arabia causing prolonged ill health, disability, early death and high health cost. Diabetes being a chronic disease causes chronic complications with high morbidity and mortality rate. To monitor this disease in the Kingdom of Saudi Arabia, a National Diabetes Registry was established in 1996. The DM registry will help in having better knowledge on the geographic distribution, the demographic characteristics and the clustering of DM in families. The DM registry will serve as an easily accessible source for data on Saudi diabetics. This will encourage researchers to study the problem of DM in the Kingdom. The aggregation, analysis and presentation of information about DM is expected

to significantly contribute to the medical understanding, demonstrating trends in management, improving the quality of care for DM patients and supporting planning and development.

#### Progress

Tables, graphs and charts have been produced in SAS® for the purpose of generating the Diabetes Registry Cumulative Report.

**Project title: PCR Assay For Detection And Quantification Of Fungal Infections In Pediatric Patients With Acute Myeloid Leukemia And Myelodysplastic Syndrome. (RAC #: 2021 054)**

**Investigators:** Rajeev K. Sathiapalan, Ibrahim Bin-Hussain, Rong Bu, Asim Belgaumi, Mohammed O. Qutub, Ahmed Al-Ahmari, Faisal Al-Kurdi, Edna Almodovar.

#### Project description

Fungal infections pose a serious challenge to survival of the child with cancer by its life-threatening nature and also compromising definitive treatment of underlying disease. Novel methods for early detection of fungi include polymerase chain reaction (PCR), galactomannan antigenemia, antibody titers and detection of fungal metabolites. Although PCR-based assays targeting unique DNA sequences have been developed for detection and identification of *Candida* and *Aspergillus* species, their application to patients at high risk for invasive mycoses is still in infancy.

A significant number of children with cancer treated at KFSH&RC and KFNC&RC develop fungal infections for unknown reasons. This longitudinal, prospective study aims at early detection of fungi by PCR assay as a surrogate marker of invasive fungal infection in pediatric patients with acute myeloid leukemia and myelodysplastic syndrome treated on acute myeloid leukemia protocol. It is expected to complement the different strategies for reducing the morbidity and mortality from fungal infections.

#### Progress

Data has been collected for 19 patients excluding the monitoring data of PCR with and without anti-fungal treatment. The database was created in SPSS and preliminary tables were submitted to Dr. Ibrahim Bin-Hussain.

**Project title: The Use Of Chlorhexidine Oral Care For The Prevention Of Ventilator-Associated Pneumonia. (RAC #: 2021 076)****Investigator:** Mohammed Hijazi**Project description**

Despite advances in the field of critical care and infection control, nosocomial pneumonia continues to be a major cause of morbidity and mortality among patients requiring mechanical ventilation and a common source of controversies among their care providers about the best diagnostic, preventive and therapeutic strategies.

Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections in intensive care units. VAP continues to complicate the source of 8 to 28% of patients receiving mechanical ventilation (MV) with mortality rate ranges from 24 to 50% and can reach 76% in some specific settings or when lung infection is caused by high-risk pathogens.

Chlorhexidine is an antiseptic solution that has been used by dentists since 1959 for the control of dental plaque. It is rapidly bactericidal to both gram-positive and gram-negative bacteria and yeast. Chlorhexidine has been studied extensively and shown to decrease aerobic and anaerobic bacteria in the oral cavity from 55 to 97% without any significant changes in bacterial resistance, overgrowth of potentially opportunistic organisms or other adverse changes in the oral microbial ecosystem.

Oral care is performed in all critically ill intubated patients. In our ICU, as in most ICUs, normal saline is used by the nurses for routine oral care. No studies evaluated the use of chlorhexidine-based oral care in the prevention of VAP in medical and non-cardiac surgical critically ill patients. Preventing VAP in this high risk group using a simple and cost effective intervention will lead to fewer days in the ICU, less antibiotic use, less cost and possibly less mortalities.

The objective of the study is to compare oral care using chlorhexidine to the routine oral care on the occurrence of VAP in mechanically ventilated medical and surgical critically ill patients.

**Progress**

Data for 346 patients were collected for this study but

only 242 cases were included when the exclusion criteria were applied. Final data management activities and statistical analysis were done. This study is completed.

**Project title: Identification Of Environmental And Genetic Factors That Influence Breast Cancer Development And Therapy In Saudi Females. (RAC #: 2031 091 KACST # ARP-2432)****Investigators:** Nasser El Kum.**Project description**

The cancer data of the Kingdom of Saudi Arabia show that breast cancer is hitting the largest proportion of the female population of the cancer patients. The high incidence and mortality rates for this type of cancer may be attributed to a number of risk factors which are to be explored for the Saudi population. We found in the Western literature that the factors showing significantly higher risks are: age at presentation; family history of breast cancer; cervix, uterus, or colon; age at first pregnancy after thirty; history of previous breast cancer; early menarche and late menopause; excessive radiation; and obesity.

Because of the lack of any original data on this subject in the Kingdom of Saudi Arabia, a case-control study is planned to be conducted at national level. This research study will describe the risk factors of breast cancer and the relationship among these factors for the Saudi population, thus, giving a better understanding of this disease in this part of the world. On the basis of this research, attempts can be made to lower both the incidence and mortality rates of breast cancer.

**Progress**

Data for 1255 patients and 707 controls has been collected and entered in an MS Access database. Data collection is ongoing.

**Project title: Prevalence Of Anemia And The Transfusion Practices In Critically Ill Patients. (RAC #: 2031 018)****Investigators:** Khalid Al Maghrabi, Rasheed Al Hubail, Mohammed Hijazi, Nabila Abouchala, Torbjorn Wetterberg, Gamal Mohammed.**Project description**

Anemia is common in critically ill patients. By day 3 of

intensive care unit admission, about 95% of the patients have hemoglobin concentration below normal. Blood transfusion and blood conservation are complementary activities that constitute the clinical arena of transfusion medicine. Recent improvement in the safety of the blood supply and the increasing costs associated with transfusion therapies have led to a reevaluation of the clinical practices of blood transfusion and blood conservation.

The transfusion practice in ICU patients is variable and the current transfusion guidelines may not be suitable for critically ill patients. The rate of transfusion in ICU ranges from 4% to 66% with an average transfusion rate of 44%. The rate of transfusion will increase with increasing length of stay in ICU. Hebert PC et al in the TRICC trial demonstrated that using transfusion trigger of 7 gm and maintaining hemoglobin concentration between 7.0-9.0 gm/dl in normovolemic patients is at least as effective as and possibly superior to a liberal transfusion strategy in which a transfusion trigger of 10.0 gm/dl and hemoglobin concentration were maintained at 10.0-12.0 gm/dl were used. With the exception of patients with acute myocardial infarction and unstable angina, using a restrictive strategy of red blood cell transfusion demonstrated a reduction in the total transfusion and decreased the chance for exposure to blood products, which carry a great importance in the presence of donor shortage and variable multiple risks associated with transfusion.

### Progress

Data for 450 patients were collected, but after application of the exclusion criteria, 6 patients were excluded. Data were entered into Excel files which were later converted into SAS. Frequency tables were generated. Statistical analysis will follow.

**Project title: Disseminated Fungal Infections Among Pediatric Patients 0-14 Years Of Age With Hematological Malignancies At KFSH&RC: A Prospective Study. (RAC #: 2041 006)**

**Investigators:** Ali Al-Ahmari, Ibrahim Bin-Hussain, Gamal Mohammed.

### Project description

Invasive fungal infections are more prevalent than ever, presenting an enormous challenge to healthcare professionals. This prevalence is directly related to the

growing population of immunocompromised individuals resulting from changes in medical practice such as the use of intensive chemotherapy and immunosuppressive drugs. In the hospital, complicated surgical procedures, widespread use of implanted devices, and the administration of a broad spectrum of antibiotics have dramatically increased the incidence of nosocomial bloodstream infections. Systemic fungal infections are a main cause of morbidity and mortality in patients with hematological malignancies.

### Progress

A 10-page data collection form has been finalized. Data for 108 patients were collected. Data were entered into an MS Access database. Data cleaning and validation are ongoing.

**Project title: Efficacy Of Combination Therapy With PEG Interferon Alfa-2a (Pegasys) Plus Ribavirin In The Treatment Of Chronic Hepatitis C: Retrospective Study. (RAC #: 2051 035)**

**Investigators:** Hamad Al Ashgar, Khalid Alsawat, Nasser El Kum, Mohammed Gaseem Khan, Saleim Dahab, Mohammed Al Fadda, Ingvar Kagevi.

### Project description

Infection with hepatitis-C virus (HCV) can result in both acute and chronic hepatitis. Acute infection is usually asymptomatic, rarely leads to hepatic failure but typically leads to chronic infection in 60-80% of cases. Chronic HCV infection is usually slowly progressive; the most common cause of chronic liver disease and the most frequent indication for liver transplantation in some parts of the world. Approximately 20-30% of chronically infected individuals develop cirrhosis over a 20 to 30-year period of time.

In Saudi Arabia the estimated seroprevalence of HCV in community-based study is estimated 1.8% similar result of 1.1% in blood donors, however, surprisingly higher prevalence in hemodialysis patients at 55-68% in one report. Genotype 4 is predominant in the Middle East and Africa.

Given data from previous studies regarding treatment of chronic HCV infection and the presence of little information in the literature with regards to genotype 4 treatment, we plan to study the experience in our hospital in the treatment of chronic HCV. It will also include

demographic and virology data for this infection.

With the introduction of the current standard therapy for chronic HCV using pegylated interferon combined with Ribavirin, we will evaluate the response rate of patients with chronic HCV.

### Progress

A 3-page data collection form has been finalized. Data collection is ongoing.

**Project title: Fever Of Unknown Origin: Experience Of A Tertiary Care Center In Saudi Arabia. (RAC #: 2061 009)**

**Investigators:** Mahmoud A. Moawad, Habib Bassil, Mona Elsherif, Mostafa Elnaggar, Jameela Edathodou, Ibtisam Baksh.

### Project description

Fever of unknown origin (FUO) is defined as a temperature higher than 38.3 degrees centigrade on several occasions and lasting longer than 3 weeks, with diagnosis that remain uncertain after 1 week of investigation in hospital or in outpatient setting. The condition represents a diagnostic challenge and as such constitutes a significant number of referrals to tertiary care centers. Previous studies have described the spectrum of the disease to be mainly secondary to infectious, neoplastic or inflammatory diseases. Between 9% and 30% in different studies end up without diagnosis despite exhaustive workup. The prognosis of these patients was found to be generally good. Occasionally, deep vein thrombosis (DVT) can present as FUO.

Diagnostic workup that starts with confirming the presence of fever in hospital and emphasizing that there is no "gold standard" test that exists for these patients is well described. Suggested minimal diagnostic workup to qualify as FUO include: complete H&P including drug history, CBCD, blood film, routine blood chemistry, urinalysis and microscopy, blood x 3 and urine cultures, ANA, RF, HIV, CMV IgM antibodies, heterophil antibody test (if consistent with mononucleosis-like syndrome), Q-fever serology (if exposure risk factors exists), CXR, hepatitis serology (if liver enzymes elevated). The role of different nuclear medicine studies (e.g. labeled leukocytes, gallium, Indium & Technitium scans) was emphasized in these patients, especially in ruling-out inflammatory conditions. In one study, immunoscintigraphy with

monoclonal antibody<sup>99m</sup>Tc-BW/250/183 sensitivity in detecting pyogenic foci was 73% and specificity was 97%, positive and negative predictive values were 93% and 87%, respectively.

With the exception of one study from Turkey, no local information is available about FUO in the Middle East. Reporting our experience should fill some of this literature gap and might be of help to our colleagues when they are faced with a patient with FUO.

### Progress

A 5-page data collection form has been finalized. Data collection is ongoing.

**Project title: Signaling Pathways Involved In Heatstroke Pathogenesis: Role Of Toll-Like Receptor-4 (TLR-4). (RAC #: 2060013)**

**Investigators:** Mohammed Dehbi, Taher Uz-Zaman, Abderrezak Bouchama, Mohammed Dehbi, Engin Baturcam, Steve Bobis, Moahamed Hassan, Sahar Salem, Ludivina Apilado, Abdelmoneim Eldali and Wilhelmina Ventura.

### Project description

In this project, we will be focusing on the molecular mechanisms governing the inflammatory, tissue injury and death responses associated with heatstroke using a mouse model. Our initial work is primarily emphasized on the role of TLR-4, a key component involved in various inflammatory responses such as sepsis, shock, burn, trauma, tissue injury and microbial infection, particularly to specific microbial components such as the endotoxin lipopolysaccharide (LPS). Our working hypothesis was based on the observation that heatstroke was associated with a release in the circulation of LPS. In addition, blocking the effects of LPS by administration of anti-lipopolysaccharide agent was shown to improve animal survival from heatstroke effects. These observations prompt us to raise the question as to whether LPS triggers or potentiates the inflammatory response observed in heatstroke cases. In an attempt to dissect this relationship, we took advantage of the availability of LPS-resistant C3H/HeJ mice, an inbred strain that resists the LPS effects due to a mutation in TLR-4. The wild type strain C3H/HeOuj is used as control.

For each strain, animals were randomly divided into 2 groups: sham-heated group, heatstroke group. Blood and

tissue samples will be collected at the onset of heatstroke and at various time points during the recovery period. Expression profiling of a panel of pro-inflammatory and anti-inflammatory mediators will be monitored. Survival rate will be established.

### **Progress**

A 2-page data collection form has been finalized. Except for the experimental data items, study data has been collected for 141 patients. Of these, 129 are included in the study while 12 were dropped due various reasons, i.e. low body temperature, underweight, died, etc. Data were entered into an SPSS database. Data collection is ongoing.

**Project title: Neuropsychology Study (RAC #: 2061 080)**

**Investigators:** Ahmed M Hassan.

### **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 of which are MRI, PET, EEG, and Neuropsychological Evaluation. Agreement among those 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**

An SQL database has been created by BESC for this study. The principal investigator himself enters the data into the database. Presently, there are 222 cases in the database. Data has been converted into SAS and SPSS for the PI to do preliminary analysis.



**CENTRE FOR CLINICAL STUDIES AND  
EMPIRICAL ETHICS**



The

## CENTRE FOR CLINICAL STUDIES AND EMPIRICAL ETHICS

The Centre for Clinical Studies and Empirical Ethics (CCSEE) has established itself as a national/regional centre of excellence for conducting bioequivalence studies and for training clinical 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. For the last 2 years, the CCSEE has been expanding in the empirical ethics and applied clinical research fields.

Recently, the Bioanalysis Laboratory of the CCSEE was accredited by the College of American Pathologists (CAP). The gross income for the year 2007 is SR 385,000.

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### *Director*

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

### *Members*

Abdelraheem Ahmed

Saleh Al-Dgither

Eman Al-Gaai, RPh, CCRP, MHHA  
(flexible employment program)

Sameer Al-Rawithi, PhD  
(on extended leave)

Reem Al-Swayeh, RPh  
(from October 2007)

Hunida Abdulhameed, RPh (from  
August 2007, grant funded)

Syed N. Alvi, PhD

Mohammad Alqaderi, RN, MSN  
Mohammed Alsunaid, MD (joint  
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Fawaz Abdullah Alturki, MD (joint  
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Sahar Atalla, MBBCH, MS (from  
October 2007)

Maria Lourdes Bautista

Kristine Concepcion, MD (from July  
2007, grant funded)

Nada Bin Hashim, RN (from July  
2007, flexible employment program)

Rajaa Hussein, RPh

Ahmed Yusuf, BSChem

## ABIOEQUIVALENCE STUDIES

### 1. Randomized, Single-Dose, Two-Treatment, Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Sildenafil Citrate 100 mg Tablet Under Fasting Conditions (RAC # 2071 058) – Ongoing

#### Results Summary

An HPLC assay for sildenafil in human plasma was developed and validated, and sildenafil stability was determined. Sildenafil and 2-hydroxycarbazole (internal standard, IS) levels were detected using Photodiode Array Detector set at 295 nm after separation on 4.6 x 150 mm, Nova-Pak C18, 4- $\mu$ m [particle-size] steel column (retention time 4.8 and 11.9 min, respectively) with a mobile phase of 0.05 M monobasic anhydrous potassium phosphate buffer and acetonitrile (70:30, v:v), pH 4.7, delivered at a flow rate of 1.2 ml/min at room temperature (RT). Plasma samples were extracted with ethyl acetate and reconstituted in the mobile phase. No interference in blank plasma or of 8 commonly used drugs was observed. The relationship between sildenafil concentration and peak area ratio (sildenafil/IS) was linear in the range of 0.02–3.0  $\mu$ g/ml, quantitation limit was 0.02  $\mu$ g/ml, intra-and inter-run coefficients of variation were < 8.2 % and < 6.9%, respectively. The recovery of sildenafil in (0.02–3.0  $\mu$ g/ml) was 92% to 104%. Sildenafil was stable for at least 24 hours at RT, 8 weeks at –20°C, or after 3 freeze-thaw cycles in plasma; for 24 hours at RT or 48 hours at –20°C after extraction; and for 48 hours at RT or 8 weeks at –20°C in water (1mg/ml).

### 2. Randomized, Single-Dose, Two-Treatment, Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Glimepiride 4 mg + metformin 1000 mg in combination vs single entity tablet under fasting conditions (RAC # 2071 059) – Ongoing

### 3. Randomized, Single-Dose, Two-Treatment, Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Glimepiride 4 mg + metformin 1000 mg in combination vs single entity tablet under fed conditions (RAC # 2071 060) - Ongoing

#### Results Summary

A rapid HPLC assay for the determination of metformin in human plasma was developed and validated, and its stability was determined. Metformin and Atenolol

(internal standard, IS) were extracted from plasma samples as follows: To 0.5 ml of human plasma sample, 15  $\mu$ g of IS in 100  $\mu$ l of deionized water, 50  $\mu$ l of 1 M HCL, and 2 ml of acetonitrile were added. The mixture was vortex-mixed and centrifuged at 4000 rpm for 10 minutes. The clear supernatant was transferred to a clean culture tube containing 2 ml of dichloromethane and vortex-mixed. After centrifugation at 4000 rpm for 10 min, 100  $\mu$ l of the clear aqueous upper layer was injected into the HPLC system. Metformin and IS were separated on a 8 X 100 mm Resolve CN, 10  $\mu$ m particle size cartridge at room temperature using a mobile phase of 0.03 M dibasic ammonium phosphate and acetonitrile (28:72, v/v) delivered at a flow rate of 2.0 ml/min. The compounds of interest were detected using a Photodiode Array detector set at 240 nm. No interference in blank plasma or of commonly used drugs was observed. The relationship between metformin concentration and peak height ratio (metformin/IS) was linear in the range of 0.05 – 5  $\mu$ g/ml, quantification limit was 0.05  $\mu$ g/ml, intra and inter-run coefficients of variation were < 3.6% and < 8.1 %, respectively. Mean recovery was 90% and 84% for metformin and IS, respectively. Metformin was stable for at least 24 hours at RT, 6 weeks at –20°C, and after 3 freeze-thaw cycles in plasma; 24 hours at RT and 48 hours at –20°C after extraction, and 48 hours at RT and 6 weeks at –20°C in deionized water.

### 4. Randomized, Single-Dose, Two-Treatment, (Generic And Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study Of Ramipril 10 mg Tablet Under Fasting Conditions (RAC Proposal # 2061 053) – Closed

#### Results Summary

A rapid, sensitive and selective LC-MS-MS assay developed and validated for ramipril determination in human plasma using Enalapril as (internal standard, IS). The method involves protein precipitation in acidic medium. A Waters Atlantis C18 column (2.1 x 100 mm, 3 $\mu$ m) and mobile phase consisting of 0.1% formic acid-methanol (10:90, v/v) were used for separation. The analysis performed by the multiple reaction monitoring (MRM) method, and the peak height of the m/z 417.3 → 234.3 transition for ramipril was measured versus that of the m/z 377.3 → 234.2 for IS to generate standard curves. No interference in blank plasma or of commonly used drugs was observed. The relationship between ramipril concentration and peak height ratios (ramipril /IS) was linear in the range of 0.5 - 80 ng/ml, quantitation limit in plasma was 0.5 ng/ml, intra- and

inter-run coefficients of variation were < 7.38 % and < 9.56 %, respectively, and recovery was 87 %. Ramipril was stable in plasma for at least 5 hours at RT, 2 weeks at -20°C, and after 3 freeze-thaw cycles in plasma; and for at least 24 hours at -20 °C after extraction.

**5. Randomized, Single-Dose, Two-Treatment, (Generic And Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study Of Simvastatin 40 mg and Ezetimibe 10 mg Combination Tablets Under Fasting Conditions (RAC Proposal # 2061 059) - Ongoing**

**6. Randomized, Single-Dose, Two-Treatment, (Generic And Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study Of Simvastatin 20 mg and Ezetimibe 10 mg Combination Tablets Under Fasting Conditions (RAC Proposal # 2061 060) - Ongoing**

**7. Randomized, Single-Dose, Two-Treatment, (Generic And Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study Of Moxifloxacin 200 mg Tablet Under Fasting Conditions (RAC Proposal # 2061 062) - Ongoing**

#### Results Summary

An HPLC assay for moxifloxacin in human plasma was developed and validated, and moxifloxacin stability was determined. Moxifloxacin and ciprofloxacin (internal standard, IS) levels were detected using Photodiode Array Detector set at 296 nm after separation on 4.6 x 150 mm, Nova-Pak C18, 4-µm (particle-size) steel column (retention time 3.9 and 9.7 min, respectively) with a mobile phase of 0.025 M ammonium dihydrogen phosphate (pH adjusted to 3.0 with phosphoric acid) and acetonitrile (80:20, v:v) delivered at a flow rate of 0.80 ml/min at room temperature (RT). Plasma samples were deproteinized using Amicon Centrifree® Centrifugal Filter Devices. No interference in blank plasma or of commonly used drugs was observed. The relationship between moxifloxacin concentration and peak area ratio (moxifloxacin /IS) was linear in the range of 0.03–10.0 µg/ml, quantitation limit was 0.03 µg/ml, intra- and inter-run coefficients of variation were < 8.4 % and < 8.1%, respectively. The recovery of moxifloxacin (0.03–9.0 µg/ml) was 92% to 96%. Moxifloxacin was stable for at least 24 hours at RT, 8 weeks at -20°C, or after 3 freeze-thaw cycles in plasma; for 24 hours at RT or 48 hours at -20°C after deproteinization; and for 48 hours at RT or 8 weeks at -20°C in mobile phase (1mg/ml).

**8. Randomized, Single-Dose, Two-Treatment, (Generic And Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study Of Irbesartan 150 mg and Hydrochlorothiazide 12.5 mg Tablet Combination Tablets Under Fasting Conditions (RAC Proposal # 2061 063) - Ongoing**

**9. Randomized, Single-Dose, Two-Treatment, (Generic And Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Irbesartan 300 mg and Hydrochlorothiazide 12.5 mg Combination Tablets Under Fasting Conditions (RAC Proposal # 2061 065) - Ongoing**

**10. Randomized, Single-Dose, Two-Treatment, (Generic And Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Diclofenac 50 mg Tablet Under Fasting Conditions (RAC Proposal # 2061 067) - Closed**

#### Results Summary

An HPLC assay for diclofenac in human plasma was developed and validated, and diclofenac stability was determined. Diclofenac and naproxen (internal standard, IS) levels were detected spectrophotometrically at 276 nm after separation on Nova-Pak C18 cartridge (retention time 3.92 and 8.30 min, respectively) with a mobile phase consisting of 0.2% glacial acetic acid and acetonitrile (51:49, v:v) and a flow rate of 2.0 ml/min at room temperature (RT). Plasma samples were extracted with tert. Butyl methyl ether and reconstituted in the mobile phase before injection into the HPLC system. No interference in blank plasma or of commonly used drugs (except for omeprazole) was observed. The relationship between diclofenac concentration and peak height ratio (diclofenac/IS) was linear in the range of 0.02 –1.92 µg/ml, quantitation limit was 0.02 µg/ml, intra- and inter-run coefficients of variation were < 5.33% and < 10.10%, respectively, and recovery was ≥ 89%. Diclofenac was stable at least for 5 hours at RT, 5 weeks at -20°C, and after 3 freeze-thaw cycles in plasma; for 16 hours at RT and 48 hours at -20°C after extraction; and for 24 hours at RT 5 weeks at -20°C in methanol.

**11. Randomized, Single-Dose, Two-Treatment, (Generic And Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Meloxicam 15 mg Tablet Under Fasting Conditions (RAC Proposal # 2061 070) - Ongoing**

**12. Randomized, Single-Dose, Two-Treatment, (Generic And Innovator) Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Ibuprofen 400 mg Tablet Under Fasting Conditions (RAC Proposal # 2071 002) - Ongoing**

**13. Randomized, Single-Dose, Two-Treatment, (Generic And Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Ketoprofen 25 mg Tablet Under Fasting Conditions (RAC Proposal # 2071 007) - Closed**

**Results Summary**

An HPLC assay for ketoprofen in human plasma was developed and validated, and ketoprofen stability was determined. Ketoprofen and diclofenac (internal standard, IS) levels were detected using Photodiode Array Detector set at 258 nm after separation on 8 x 100 mm, 8 Nova-Pak C18, 4- $\mu$ m (particle-size) cartridge (retention time 4.1 and 8.7 min, respectively) with a mobile phase of 0.20% glacial acetic acid (pH adjusted to 3.0 with phosphoric acid) and acetonitrile (50:50 v:v) delivered at a flow rate of 2.0 ml/min at room temperature (RT). Plasma samples were extracted with tert. butyl methyl ether and reconstituted in the mobile phase. No interference in blank plasma or of commonly used drugs was observed. The relationship between ketoprofen concentration and peak area ratio (ketoprofen/IS) was linear in the range of 0.02–10.0  $\mu$ g/ml, quantitation limit was 0.02  $\mu$ g/ml, intra- and inter-run coefficients of variation were < 5.7 % and < 8.1%, respectively, and extraction recovery was 90% to 99%. Ketoprofen was stable for at least 24 hours at RT, 10 weeks at –20°C, or after 3 freeze-thaw cycles in plasma; for 24 hours at RT or 48 hours at –20°C after extraction; and for 48 hours at RT or 10 weeks at –20°C in methanol (1 mg/ml).

**14. Randomized, Single-Dose, Two-Treatment, (Generic And Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Glybenclamide 5 mg Tablet Under Fasting Conditions (RAC Proposal # 2071 017) - Closed**

**Results Summary**

A rapid HPLC assay for glybenclamide in human plasma was developed and validated, and glybenclamide stability was determined. Glybenclamide and Ketoconazole (internal standard, IS) were extracted from plasma as follows: 0.25  $\mu$ g of IS and 50  $\mu$ l of 1 M HCL were added to 0.5

ml of plasma, shaken for 10 seconds, and extracted with 5 ml (methylene chloride and hexanes 50/50, v/v). The organic layer was transferred to a clean tube, and dried under a gentle stream of nitrogen at room temperature. The residue was reconstituted in 200  $\mu$ l mobile phase, and 100  $\mu$ l of that was injected into the HPLC system. Glybenclamide and IS were separated at room temperature on a Symmetry RP18, 5 $\mu$ m column using a mobile phase of 0.05 M dibasic ammonium phosphate (pH 5.5) and acetonitrile (50/50 v/v) delivered at a flow rate of 1 ml/min. A 2475 multi-lambda fluorescence detector at an excitation and emission wavelengths of 235 and 354  $\mu$ m, respectively, detected the compounds of interest. The relationship between glybenclamide concentration and peak area ratio (glybenclamide /IS) was linear in the range of 0.01 – 0.60  $\mu$ g/ml, quantification limit was 0.01  $\mu$ g/ml, intra and inter-run coefficients of variation were 1.2% to 5.9% and 2.5% to 6.5%, respectively, and recovery was 91%. Glybenclamide was stable for at least 24 hours at RT, four weeks at –20°C and after 3 freeze- thaw cycles in plasma; for 24 hours at RT and 48 hours at –20°C after extraction, and for 48 hours at RT and 2 weeks at –20°C in methanol.

**CLINICAL STUDIES**

**1. Measuring Placebo Effect by Elimination and Investigating Its Mechanism of Action (RAC Proposal # 2051 0072) – Ongoing**

**Project description**

Placebos have been in use for centuries in medical practice. However, there is continued controversy regarding their effectiveness and mechanisms of action. We propose to measure the effect of placebo by a novel design, determine its interaction with the effect of active drug, and explore whether placebo exerts part of its effect at the pharmacokinetics level.

**2. Sodium Bicarbonate in Preventing Contrast Induced Nephropathy (SIPCIN): A Randomized Controlled Study. (RAC # 2071 003) – Ongoing**

**Project description**

Contrast-induced-nephropathy (CIN) is not a uncommon disease that is associated with important morbidity and mortality, particularly in high risk patients. The study of choice to prevent CIN has not been established.

Traditionally, intravenous of normal saline (1 ml/kg/hr for 12 hours before, during, and 12 hours after, procedure) has been used. Sodium bicarbonate infusion (150 mEq/L, 3.5 ml/kg/hr for 1 hour before procedure and 1.2 ml/kg/hr during and for 5 hours after procedure) has recently been shown to be associated with impressive results; however, it has been adopted by the medical community for several reasons. We plan to conduct an open label, randomized, and stratified, parallel-group study to compare normal saline infusion to sodium bicarbonate infusion. 220 adult patients scheduled for routine cardiac catheterization will be enrolled. They will stratified according to the presence or absence of DM, or an estimated GER of less than 60 ml/hr before being block-randomized to the two groups. The incidence of CIN will be determined based on the average of two measurements of creatinine level before and 48 hours after the procedure, and an increase of 25% or .05 mg/dL (44.2 µmol/L) or more. The data will be analyzed by the chi square test. It is expected that the results will establish whether the more practical strategy of sodium bicarbonate infusion is indeed superior to the traditional strategy of normal saline infusion. The results will have obvious clinical implications on CIN prevention in KFSH & RC and worldwide.

### **3. Pain among King Faisal Specialist Hospital and Research Centre Cancer Patients: Prevalence, Severity, Impact on Quality of Life and Adequacy of Management (RAC # 2071 028) - Ongoing**

#### **Project description**

The purpose of this study is to systematically explore pain prevalence, severity, impact on quality of life, and adequacy of management among King Faisal Specialist Hospital and Research Centre (KFSH&RC) cancer patients during hospitalization. 200 consecutive patients will be studied and data will be collected through semi-structured interview and the following instruments: (a) Demographic data sheet (DDS), (b) Brief Pain Inventory (BPI), (c) The World Health Organization Quality of Life – brief (WHOQOL), (d) Memorial Symptom Assessment Scale (MSAS), and (e) Pain Management Index (PMI).

### **4. How Much Do Outpatients Know About their Medications? (RAC # 2071 077) – Ongoing**

#### **Project description**

Patients need to adhere to their medications to optimize benefits. Medication knowledge (MK) is one of the most

important determinants of adherence. Without adequate MK, medications can be ineffective and even risky. We plan to survey 1000 adult patients (or caregivers) attending outpatient pharmacy of KFSH&RC, Riyadh, to assess their MK using an investigator-administered questionnaire that was based on the MedTake test tool. Participants' MK will be compared to the information on the label of the medications bag as well as individual medication label. The degree of discrepancy will be correlated with literacy, number of medications, as well as socioeconomic and demographic characteristics of participants. The results are expected to shed light on the extent of lack of MK and to identify areas in need of improvement in order to optimize health outcomes.

### **5. Salivary Testosterones Level in Healthy Male Arabs (RAC # 2071 081) – Ongoing**

#### **Project description**

Accurate determination of biologically-available testosterone levels is fundamental to studying physiological and pathological androgenic status. Measuring salivary testosterone level is convenient, non-invasive, and accurate. We plan to develop and locally validate a liquid chromatography assay for salivary testosterone and use it to determine normal testosterone levels in adult Arab males of different age groups. The magnitude of periodic and diurnal variation will also be determined. 1000 healthy males divided into 5 equal age groups will be recruited through advertising within and outside KFSH&RC. The assay will be fully validated according to the FDA standards. After undergoing a screening history and physical examination, volunteers will be given a special sampling device to collect 1.5-2 cc of saliva, store it as needed at 2-8°C, and bring it within 2 days to the CCSEE. The mean (SD, range) of testosterone level will be calculated for each age group. Testosterone level among age groups will be compared using ANOVA. Diurnal variation will be assessed by two-tailed paired t-test. Periodic variation will be assessed by ANOVA. The results of the study will provide a validated assay as well as the normal reference values of testosterone in male Arabs that can be used in clinical practice and future clinical research. They will also indicate the degree of periodic and diurnal variation in salivary testosterone level.

### **6. Generic Formulations of Commonly-Used, Immediate-Release, Solid, Oral, Drugs in Saudi Arabia: Interchangeability and Post-Marketing Quality (RAC Proposal # 2071 001) – Closed**

## EMPIRICAL ETHICS STUDIES

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### **1. Modeling Ethical Resolution: Mapping Points of Ethical Equilibrium (RAC # 2060 004) - Ongoing**

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

### **2. Ethical Approval of Human Subjects Published in Saudi Medical Journal (RAC Proposal #2051 030) – Ongoing**

#### **Project description**

Much attention has recently been devoted to strengthening the safeguards for research subjects. This study will provide information essential in evaluating the ethical quality of research done in Saudi Arabia.

### **3. Medical Chaperoning at KFSH&RC: Physicians' View (RAC # 2071 011) - Ongoing**

#### **Project description**

There are many international guidelines, advices or policies that have addressed the issue of medical

chaperoning, but variation and inconsistencies between individual practicing physicians still exist. We plan to study physicians' views and examine practices at KFSH&RC of medical chaperoning, identify factors that influence the use of chaperones, examine physician's perception of chaperoning in general and examine reasons for use (or none use) of chaperones. We will use a survey tool consisting of 18 questions in total and will be distributed during medical Grand Rounds. All data collected will be treated as highly confidential.

### **4. Public View on Consenting for Retrospective Research on Medical Records and Leftover Tissues (RAC # 2071 031) – Ongoing**

#### **Project description**

Retrospective research utilizing medical records and/or leftover tissue samples has played an essential role in generating scientific hypothesis to be examined prospectively. Although the requirement of a consent is the default in any individually identifying biomedical research, the "level" of consenting required for retrospective research continues to be controversial. A paternalistic approach aiming to safeguard the scientific integrity of the data maintains that an implicit consent should be adequate (opt-out approach). A "rights" approach emphasizing autonomy demands an explicit consent (opt-in-approach). The few studies that have explored the public view on the issue revealed that it may be culture-specific. No study has explored the public view in the Islamic/Arabic culture. Further, few studies has explored the public view in the Islamic/Arabic culture. Further, few studies have directly compared the views of patients and health care professionals' in the same culture.

### **5. Disclosure of Medical Errors: KFSHRC Patients and Physicians Attitudes (RAC # 2071 054) – Ongoing**

#### **Project description**

A critical step toward improving safety of the health care system is to ensure that it is aware of its errors. Patients and their families are an integral part of the system. Although ethical and clinical practice guidelines advocating disclosure of medical errors to patients and families have been issued, they are in general based on little empirical evidence and have not been satisfactorily implemented. The purpose of this study is to explore

the views and attitudes of KFSH&RC's patients and physicians on disclosure of medical errors to patients/families; what is personally preferred, generally required, and currently practiced. Data will be collected from 1000 patients and all physicians or Saudi physicians at KFSH&RC. It will be collected using self (physicians) or investigator (patients) administered questionnaires that have been developed based on Guttman scaling. The results are expected to aid policy makers to develop evidence-based disclosure guidelines and identify obstacles for their application.

#### **6. Consenting Options for Organ Donation: A Survey of the Opinion and References of Saudis (RAC # 2071 068) – Ongoing**

##### **Project description**

There is a huge gap between organ supply and demand worldwide. Despite being the predominant source, cadaveric organ donation is limited, mainly because of failure to obtain consent. The consenting process currently used in Saudi Arabia is explicit consent. Other types of consenting that may improve organ procurement are potentially available. We aim to study the opinions and preferences of the Saudi public in regards to several types of consenting. 1000 Saudi adults (including patients and their companions) at the outpatient clinics of KFSHRC will be approached to complete self- or investigator-administered questionnaire. Pertinent demographic data will be collected and correlated with responses. This study is expected to provide ethicists and policy makers with important information on acceptable ways to improve the consenting rate for organ donation. It will also help formulate a Saudi public view and thus contribute to the global bioethics view on organ donation.

#### **7. Patients' Perception of Informed Consent: Function and Required Information (RAC # 2081 002) – Ongoing**

##### **Project description**

The informed consent (IC) is an established ethical and legal requirement for providing medical care. IC can be general or specific, implicit or explicit, and written or verbal, depending mainly on the intervention provided. The "function" of IC and the type and extent of information to be provided continue to be controversial.

As part of our empirical ethics program, we plan to explore the perception of KFSH&RC's adult patients about the current and desired function of procedure-specific, explicit, written informed consent. We will also explore their perception of the current (and desired) type and extent of information provided. 650 individuals representing KFSH&RC adult patients who had, or are going to have, surgery or a medical procedure will be recruited in the outpatient setting. An eight-page questionnaire developed by the investigators will be self- or investigator-administered in Arabic. The questionnaire will be pre-tested on 20 patients. The response rate will be determined and data will be tabulated and related to type of procedure and patient's age, gender, health status, occupation, and level of education. The results of the study are expected to provide an empirical evidence of patients' perceptions and expectations of the IC that will help physicians/policy makers in educating patients, improving patient's satisfaction, and obtaining a "true" IC.

#### **TRAINING AND EDUCATION**

- a. Clinical Research Professionals' Course – 38 students enrolled in May 2007 and 33 students in January 2008
- b. LC-LC/MS Comprehensive Training Course – planned for 05-09 April 2008

## PUBLICATIONS

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- Hussein R, Lockyer M, Yusuf A, Al-Gaai E, Abdelgaleel A, and Hammami MM. Bioequivalence Assessment of Two Domperidone Tablet Formulations. *Drug Research*. 2007;57(5):269-273.
- Al Hawari S, Al-Gaai E, Yusuf A, Abdelgaleel A, and Hammami MM. Bioequivalence Study of Two Metformin Formulations. *Drug Research*. 2007;57(4):192-195.
- Hussein R, Lockyer M and Hammami MM. Bioequivalence Assessment of Two Capsule Formulations of Omeprazole in Healthy Volunteers. *Drug Research*. 2007;57(2):101-105.
- Al-Gaai E, Omer H, and Hammami MM. Medical Chaperoning at a Tertiary Care Hospital in Saudi Arabia: Prevalence and Patient Preference. *Annals of Saudi Medicine* 2007;27(3):217-219.
- Alvi S, Al-Dgither S, and Hammami MM. LC-MS/MS Electrospray Ionization Validated Assay for the Determination of Ramipril Stability in Human Plasma. Presented at the Analytical Research Forum 2007, 16-18 July 2007, University of Strathclyde, United Kingdom.

# **COMPARATIVE MEDICINE**



The Department of

# COMPARATIVE MEDICINE

The mission of the Department of Comparative Medicine (DCM) is to assist the research activities of the Hospital and Research Centre by:

- a. Providing animals and veterinary care for a wide variety of species (from rodents to primates).
- b. Offering an array of technical services and expertise by highly qualified staff (veterinarians, scientists and technicians).
- c. Offering teaching in animal use for research and participating in experimental surgery courses with other departments (Neurosciences, General Surgery, Obstetric Gynecology, Urology)

The DCM also conducts in-house research activities in areas pertinent to the Kingdom of Saudi Arabia such as heatstroke, tuberculosis and cardiovascular diseases.

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*Director*  
**Abderrezak Bouchama, MD**

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*Administrative Staff*  
Perlie F. Bohol  
Ma. Cecilia Badajos

## EXPERTISE

- a. Development and/or provision of various animal models of important human diseases including transgenic mice
- b. Expertise in veterinary care for a large variety of laboratory animal species including rats, mice, rabbits, cats, guinea pigs, hamsters, sheep, dogs and baboons.
- c. Expertise in conducting both clinical and basic research (heatstroke, sepsis, infectious diseases).
- d. A well equipped surgical theatre for general laparoscopic, micro- and cardiovascular surgery for research and training
- e. A microsurgery suite equipped with latest generation of microscopy

## SIGNIFICANT ACHIEVEMENTS

Below is the 2007 highlight:

- a. 1 pre-clinical trial was successfully conducted/ completed (in collaboration with Eli-Lilly)
- b. 3 new proposals were submitted/approved
- c. 7 papers were published
- d. 3 papers were submitted
- e. 4 Abstracts were accepted/presented
- f. 6 presentations/seminars were provided (1 local and 4 overseas)
- g. Recognition of KFSH&RC by the WHO  
\*KFSH&RC a centre of excellence in environmental health
- h. 2 new international collaborations were initiated
- i. 2 veterinary staff joined the Department
- j. Reorganization of the Animal Core Facility was successfully executed

- k. 7 workshops were provided (209 participants)
- l. Educational trainings (12 participants)

## RESEARCH ACTIVITIES

The DCM had a very productive year 2007 either measured by:

- 1. Newly approved or active projects
- 2. Extramural fundings
- 3. Publications
- 4. Meetings presentations

## NEWLY APPROVED OR ACTIVE PROJECTS

The DCM had 3 approved projects in 2006/2007 namely:

- a. RAC# 2070 O15. Genomic and proteomic profiling of heatstroke in a mouse model
- b. RAC# 2060 O13. Signaling pathways involved in heatstroke pathogenesis in mice model
- c. KACST Project AT-25-86. Surveillances, studying epidemiological drug resistance TB and their impact on National Tuberculosis Program (NTP)

This is in addition to the on-going projects approved on the previous years.

	Newly Approved Projects	Active Projects	TOTAL
RAC	2	1	3
KACST	1	4	5
Other (Riyad Bank)		1	1
<b>TOTAL</b>	<b>3</b>	<b>6</b>	<b>9</b>

## Extramural Funding

The DCM has secured a remarkable SAR 5.72 million grant from various funding sources. This emphasizes the competitiveness and the quality of research produced in the department.

Sponsor	Project & Investigator	Active Grants
KACST	Surveillances, Studying Epidemiology of Drug Resistance TB & their impact on the national TB Program (Dr. Hajoj)	934,000 SAR
KACST	Brain injury in heatstroke: Study using diffusion MRI, MR-spectroscopy & PET in baboons (Dr. Bouchama)	1.5 Million SAR
KACST	Coagulation & Fibrinolysis Response Patterns to Severe Heatstroke and its Relation to Inflammation and Cell Injury in Baboon Model (Dr. Bouchama)	316,000 SAR
Eli-Lilly	Effect of recombinant APC on inflammatory & Haemostatic responses in primates suffering from lethal heatstroke (Dr. Bouchama)	163,713 SAR
KACST	Molecular Epidemiology of TB in Saudi Arabia (Dr. Hajoj)	1 Million SAR
Riyad Bank	Molecular Basis of Drug Resistant TB in Saudi Arabia (Dr. Hajoj)	1.8 Million SAR
TOTAL		5.72 Million SAR

## PUBLICATIONS

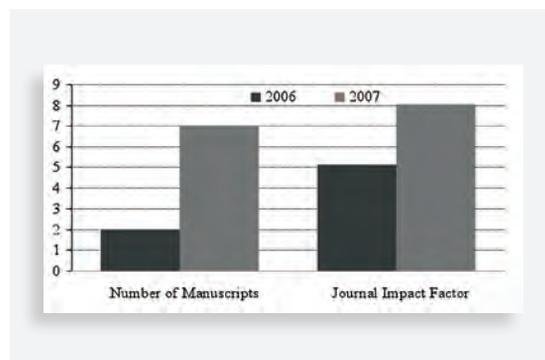
Both the number and the quality of publications (measured by impact factor) has remarkably improved as compared with 2006.

- Bouchama A, Dehbi M, Mohamed G, Matthies F, Shoukri M, Menne B. Prognostic Factors in Heat Wave-Related Deaths: A Meta-analysis. *Arch Intern Med.* 2007;167:2170-2176.
- Bouchama A, Dehbi M, Chaves-Carballo E. Cooling and hemodynamic management in heatstroke: practical recommendations. *Crit Care.* 2007;11:R54.
- Bouchama A, Kwaasi A, Dehbi M, Al Mohanna F, Eldali A, El-Sayed R, Tbakhi A, Alzahrani AS, Roberts AG. Glucocorticoids do not protect against the lethal effects of experimental heatstroke in baboons. *Shock.* 2007;27:578-583.
- Al-Hajoj SA, Zozio T, Al-Rabiah F, Mohammad V, Al-Nasser M, Sola C, Rastogi N. A First Insight on the

Population Structure of Mycobacterium tuberculosis in Saudi Arabia. *J Clin Microbiol.* 2007;45:2467-73.

- Al-Hajoj SA, Al-Rabiah F. Is Saudi Arabia a fertile land for exchanging infectious diseases? *Saudi Med J.* 2007;28:803-4.
- Al-Hajoj SA, Mohammed VK, Al-Hokail AA. Usefulness of molecular techniques to identify ongoing tuberculosis transmission in Saudi Arabia. *Saudi Med J.* 2007;28:268-270.
- Mistrello G, Harfi H, Roncarolo D, Kwaasi A, Zanoni D, Falagiani P, Panzani R. Date Palm Pollen Allergoid: Characterization of Its Chemical-Physical and Immunological Properties. *Int Arch Allergy Immunol.* 2007;145:224-230.

## Publications Summary: 2006 versus 2007



## Submitted Publications

- Bouchama A, Kunzelmann C, Dehbi M, Kwaasi A, Eldali A, Zobairi F, Freyssinet JM, de Prost D. Recombinant human activated protein C attenuates endothelial injury and inhibits procoagulant microparticles release in baboon heatstroke. (Submitted to *Journal of Thrombosis and Haemostasis*)
- Roberts G, Chishti M, Al-Mohanna F, El-Sayed R, Bouchama A. Microvascular injury, thrombosis & inflammation underlie the pathogenesis of heatstroke: A study in baboon. (Submitted to *Artherosclerosis, Thrombosis & Vascular Biology*)
- Al-Hajoj S, Batt S, Al-Rabiah F. Tuberculosis in Saudi Arabia. How little we know? How little we do? The need of a new strategy to control the disease. (Submitted to *Saudi Medical Journal*)

**Meeting Presentations (Presented/Accepted)**

The DCM staff participated actively on both national and international meetings.

Research Unit	Number of Posters	Countries
Heatstroke	2	USA (1) KSA (1)
Tuberculosis	2	Greece (1) Netherlands (1)
Comparative Pathology	1	Germany
<b>TOTAL</b>	<b>5</b>	<b>5 Countries</b>

**Conferences/Seminars**

- a. 20<sup>th</sup> European Society of Intensive Care Medicine Congress (Oct. 7-10, 2007), Berlin, Germany. Dr. Abderrezak Bouchama
- b. 2<sup>nd</sup> International Pan-Arab Critical Care Medicine Congress (Apr. 20-24, 2007), Dubai, UAE. Dr. Abderrezak Bouchama
- c. WHO 3<sup>rd</sup> Meeting on Improving Public Health Responses to Extreme Weather events (Mar. 22-23, 2007), Bonn, Germany. Dr. Abderrezak Bouchama
- d. WHO Advisory Committee Meeting (Jan. 18-20, 2007), Roma, Italy. Dr. Abderrezak Bouchama
- e. Tuberculosis in Saudi Arabia: How Little We Know, How Little We Do (May 14, 2007) Dept. of Medicine Medical Grand Rounds, KFSH&RC. Dr. Sahal Al-Hajj

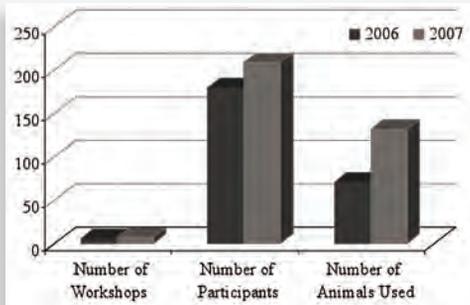
**ACADEMIC TRAININGS AND WORKSHOPS**

The number and variety of workshops and educational trainings offered by the DCM in collaboration of various hospital departments continue to increase as compared with 2006.

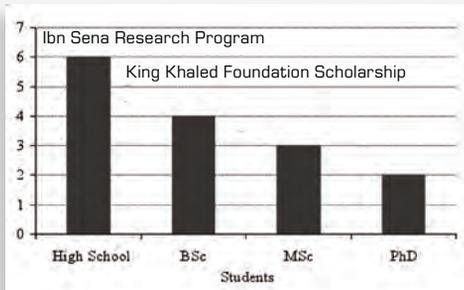
**WORKSHOPS**

Activities	Number of Participants	Number of Animals Used
Microsurgery Course (2 workshops)	10	105 rats
2nd International Difficult Airway Management Workshop	80	8 dogs
Residents Laparoscopic Workshop	20	4 dogs
Residents Anastomosis Workshop	40	3 dogs and 3 sheep
Residents Anastomosis & Laparoscopic Workshop	36	4 dogs and 4 sheep
Life Support Training Center	23	1 sheep
<b>TOTAL</b>	<b>221</b>	<b>132</b>

**Workshops Summary: 2006 versus 2007**



**Training and Educational Activities**



**COLLABORATIONS**

The DCM has developed a large network of collaborators both locally and internationally.

**National**

- a. KFSH&RC, Riyadh
- b. National Guard Hospital, Riyadh
- c. National Commission for Wildlife Conservation and Development, Taif

**International**

- a. United States of America: Eli-Lilly & Company, Indianapolis
- b. Canada: University of Toronto, Toronto
- c. Netherlands: National Institute of Public Health & Environment
- d. World Health Organization: European Centre for Environment and Health
- e. France:
  - 1. INSERM, Paris
  - 2. Hopital Louis Mourrier, Paris
  - 3. Universite Louis Pasteur, Strasbourg
  - 4. Institut Pasteur de Lille, Lille
  - 5. Institut Pasteur de Guadeloupe, Guadeloupe
- f. United Kingdom: Royal Free University, London

## **OTHER ACHIEVEMENTS**

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- a. Construction of a new DCM with modern architecture and design was started
- b. Laparoscopic and 1 Microsurgery Suite acquired
- c. 2 new senior veterinarian staff were recruited
- d. Project of establishing a breeding baboon facility in collaboration with National Commission for Wildlife Conservation & Development, Taif is under discussion

## **FUTURE GOALS**

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- a. Launch the first high throughput cytokine profiling Platform
- b. Launch the first high throughput biomolecular interactions platform
- c. Strengthen the collaborations and links
- d. Establishment of a baboon breeding facility
- e. Focus on translational research by conduct more pre-clinical trials on relevant species
- f. Establishment of Veterinary Diagnostic Lab

## Research Unit

# EXPERIMENTAL SURGERY, ANIMAL FACILITY

The primary function of Animal Experimental Surgery (AES) is to assist investigators and surgeons in their obligation to plan and conduct animal surgery, experiments in accord with the highest scientific, humane and ethical principles. Opportunities also exist for collaborative research and training of resident physicians from various KFSH & RC departments.

The Experimental Surgery program is designed to help the enhancement of surgical skills of surgeons in various disciplines. The section supports surgical research aimed at developing and utilizing new techniques, devices and instruments for improving patient care. The programme provides training and workshops in all areas of surgical disciplines.

A modern surgical theatre, fully equipped with all the auxiliary facilities for general surgery, cardiovascular surgery, laparoscopic and neuro-surgery.

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### *Head*

**Ra'afat M. El-Sayed, DVM, MVSc**

### *Members*

Falah H. Al-Mohanna, DVM

Mohammed Hassan, DVM (RC  
Grant)

Ludivina A. Apilado

Sahar I. Salem

Merfat A. Elyan

## SERVICE WORK

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The Experimental surgery suite is equipped with state of the art anaesthesia machines and monitoring equipments to ensure the success of all surgical procedures, heart- lung machine, defibrillator, diathermia, Pulse ox meter, echocardiogram, urodynamic machine, blood gas machine, haematology analyzer and other relevant instruments are in place. Fluoroscopy, Laparoscopy and Endoscopy equipments and facilities are also available. Expertise is also available to support routine and specialized surgical procedures.

- a. Provide support and services for experimental surgery requirements of various research
- b. Provide opportunities and support for the development and practice of new surgical teaching and training programs at KFSH&RC, techniques on animal models for implementation to rectify malfunctioning organs or tissues.
- c. Well-equipped surgical theatres, facility and staff are available to provide for major surgical research obligations in cardiovascular, general, dental, laparoscopic, transplantation, microsurgery, neuroscience and urological surgery subspecialties.

## TRAINING & WORKSHOPS

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The Experimental Surgery Staff collaborate with staff from various departments of the hospital and Research Centre to provide support and services for experimental surgery requirements of approved various research, and offer training and workshops that were attended by participants from Saudi Arabia and overseas in the following disciplines:

- a. Microsurgery
- b. Laparoscopy
- c. Endoscopy
- d. Bowel Anastomosis
- e. Vascular Surgery
- f. General surgery procedures
- g. Difficult Airway Management

### Objectives

- a. To promote & improve surgical practice.
- b. To enhance the knowledge of new skills and

- techniques in minimally invasive surgery
- c. To improve communication and interaction among healthcare providers.

## Surgical Theatre

The theatre can accommodate 4 experimental surgical working stations. Each working station is composed of:

- a. An operating table
- b. Instrument table with all necessary surgical instruments
- c. Anaesthesia machine
- d. Endoscope camera coupled with a cold light source
- e. TV monitor
- f. Insufflator
- g. Vacuum suction irrigation system

## Training in Microsurgery (Microsurgery Animal Lab)

The Microsurgery Laboratory at CMD, KFSH&RC in collaboration with the departments of Neuroscience offer two types of courses:

- a. A continuous course held on Sunday and/or Wednesday mornings for hospital staff and candidates who live in the Riyadh area.
- b. The Intensive courses are given 4 times a year and each section runs for five consecutive days for a total of 40 hours. Participants who achieve the required level of competence after satisfactory completion of at least 30 hours of hands-on practice in the relevant microsurgery procedures are issued with certificates.

Microsurgery Animal Lab is equipped with 6 microscopes with video camera and LCD TV.

The following departments use the Microsurgery Animal Laboratory:

- a. Department of Neurosurgery
- b. Department of Urology
- c. Department of Plastic Surgery
- d. Cardiovascular Department

## Training in Laparoscopy (Laparoscopy Animal Lab)

Minimal invasive surgical training programs are offered in different Laparoscopic and Thoracoscopic procedures

in collaboration with the departments of Surgery.

The duration of the program, which is offered 4 times a year, is between 1 & 3 days for a total 10 to 30 hours. Training includes the following:

- a. Intra-abdominal orientation is carried out from diaphragm to the pelvis, learning tactile and feedback and depth perception.
- b. Once the candidate is comfortable with that aspect of training (orientation), they will proceed with some actual procedures, which will involve:
  - 1. Appendectomy; removal of appendix
  - 2. Cholecystectomy; removal of gall bladder
  - 3. Splenectomy; removal of spleen
  - 4. Nissen fundoplication.
- 5. Gynecology: Tubal Ligation, Ovarian Cystectomy, Oophorectomy, Vaginal Hystrectomy Pelvic Lymphadenctomy
- 6. Bowel Anastomosis: stapling techniques (side to side, end to end and combined techniques), Tracheostomy, Laparotomy, Gastrectomy, Aortotomy with vein patch, Knot (basic knot, square knot two-hand and one-hand technique) and Robotic bench work: set-up, scopes and robotic suturing.

The following attendants use the Laparoscopy Animal Laboratory:

- a. Minimally Invasive & Robotic Surgeons.
- b. General & Specialist Surgeons.
- c. Residents.
- d. Doctors interested in minimally invasive surgery.
- e. Other health care providers.

**Training in Bowel Anastomosis, Vascular Surgery & General surgery procedures**

- a. Vascular Surgery:
  - 1. Dissection of Carotid Artery and Jugular vein
  - 2. A.V. Fistula Creation

- 3. Closure of carotid defect
- b. Gastrointestinal orientation and exploratory examination.
- c. Gastro Enterotomy
- d. Gastrectomy
- e. Roux En Y Reconstruction
- f. Bowel Resection & Anastomosis

**FACTS AND FIGURES**

Workshops Performed in Year 2007

Training & Workshops	Details
Microsurgery, Intensive Course	2 courses, 105 rats 10 participants
2 <sup>nd</sup> International Difficult Airway Management workshop	1 workshop, 1 dog +7 sheep 80 participants
Laparoscopy and Bowel Anastomosis for Residents	1 workshop, 2 dogs+ 2 sheep 30 -32 participants
Laparoscopy and Bowel Anastomosis for Residents	1 workshop, 3 dogs+ 3 sheep 38-40 participants
Bowel Anastomosis & General Surgery procedures	1 workshop, 4 dogs + 4 sheep 36-40 participants
Life Support Training Fundamental of Critical Care Support	20-23 participants 1 sheep
<b>TOTAL</b>	<b>Participants : 214-225 Dogs: 10 Sheep:17 Rats: 105</b>

Training & Workshops / RAC #	Principal Investigator / Department	Date	# of Participants	Animals Used
Bowel Anastomosis, Airway Management, Vascular procedures and Laparoscopy RAC # 2032 002	Drs. Alaa Abdul Jabbar & O' Regan / Dept. of Surgery	1st February 2007	38 participants 8 instructors + 2 OR nurses + 7 LAF staff (in 2 sessions)	3 dogs & 3 sheep
Life Support Training Centre: Fundamental of Critical Care Support	Dr. Sulaiman Al Hosaini	12-14 February 2007	23 participants	1 sheep
2 <sup>nd</sup> International Difficult Airway Management Workshop ACUC# 2072 001	Dr. Hossam Al Oufi Dept. of Anaesthesiology	10-11 April 2007	80 participants 10 Instructors 4 anaesth. tech 7 LAF staff 2 days 2 sessions/day	1 dog & 7 sheep
Bowel Anastomosis, General Surgery Procedures and Laparoscopy RAC # 2032 002	Drs. Alaa Abdul Jabbar & O' Regan / Dept. of Surgery	17 May 2007	32 participants 6 instructors 2 OR nurses + 7 LAF staff (in 2 sessions)	2 dogs & 2 sheep
Bowel Anastomosis, Vascular Procedures, And General Surgery Procedures RAC # 2032 002	Drs. Alaa Abdul Jabbar & O' Regan / Dept. of Surgery	08 November 2007	36 participants 6 instructors + 2 OR nurses + 7 LAF staff (in 2 sessions)	4 dogs & 4 sheep
Microsurgery Intensive Course RAC # 2022 008	Dr. Essam Al Shail / Dept. of Neurosciences	26-30 May 2007	4 participants 1 instructor	53 rats
Microsurgery Intensive Course RAC # 2022 008	Dr. Essam Al Shail / Dept. of Neurosciences	1-5 December 2007	4 participants 1 instructor (One from Germany)	52 rats

## RESEARCH PROJECTS

The Surgical staffs collaborate with and facilitate the research of surgeons and clinicians at KFSH&RC. The unit collaborates with several departments within the hospital such as Cardiovascular Diseases, Neurosciences, Obstetrics and Gynaecology, Radiology, Surgery and Urology as summarized below:

Research Project/P.I./ Department	No. of Animals Used	RAC Approved No. of Animals
RAC# 2060 019. Evaluation of a Modified Technique of Heterotopic Heart Transplantation in Dog & Rat. Dr. C. Canver. King Faisal Heart Institute	5 dogs 5 rats	6 dogs 6 rats
RAC# 2050 032. The Effect of $\alpha$ Adrenergic Blockers on the Ureter: An <i>in vivo</i> Study in the Dogs. Dr. R. Seyam. Dept. of Urology	19 dogs	20 dogs
RAC# 2031 086. Optimization of <i>Tunica Albuginea</i> Free Graft for Coporoplasty, An Experimental Baboon Animal Study. Dr. R. Seyam. Dept. of Urology	14 baboons	26 baboons
RAC# 2031 019. Establishing Atrioventricular Synchrony in Dogs With Surgically Created Complete Atrio-Ventricular Block. Dr. M. Al Fayyadh. Dept. Cardiovascular	7 dogs	10 dogs
RAC# 2050 020. Maximum Tissue Temperature and Propagation of Heat in Knee Joint and Soft Tissue After Application of Ultrasound Therapy Versus Low Level Laser in Dogs. Dr. S. Sabbahi. Dept. Physical Therapy	6 dogs	10 dogs
RAC# 2030 088 Phase I & II. Myocardial Infarct Model in Baboons. Dr. C. Mullangi. King Faisal Heart Institute	10 baboons 17 cardiac surgery	10 baboons

## Achievements in 2007

- Renovated Microsurgery Animal Lab and equipped with 6 new Leica microscopes with video camera and LCD TV and new microsurgical instruments.
- Receiving of a complete laparoscopic tower set as a donation to Research Centre from Al Mohandas Trading Establishment, on May 15 2007.

## Future Plans

- Furthermore, work is in progress to establish additional laparoscopic surgical theatres Linked by an interactive multimedia teaching system, which displays different kinds of images, surgical laparoscopic procedures and endoscopic view.
- To establish a training centre in collaboration with the Departments of and Surgery, Neuroscience and Cardiovascular Surgery at King Faisal Specialist Hospital and Research Centre.



Research Unit

# HEATSTROKE

Heatstroke is a public health problem in Saudi Arabia, during the pilgrimage to Makkah, especially when it falls into the hot cycle of the year. For example in August 1985, there were 2,000 cases of heatstroke of which 1,000 died in temperate climates. Severe heat waves have recently led to an unprecedented 70,000 in Europe, of which a third was due to heatstroke. As sophisticated climate model predicts an increasing frequency and severity of heat-waves, the incidence of heatstroke with an outcome of mortality or neurologic morbidity is expected to rise if in addition to preventive measures, novel therapy are not developed. Heatstroke unit has been performing clinical and experimental research on the molecular and cellular mechanisms of tissue injury in heatstroke for almost 20 years with the perspective of discovering novel therapies. This accumulated experience has earned the unit a worldwide recognition underlined by our designation as a full member of the advisory board of the WHO environment and health, Europe. We have also been asked to draft, a working document on the effect of heat on health and the protection of the population to this emerging environmental threat. When these recommendations will be officially endorsed by the WHO, this will be a major accomplishment for the Research Centre.

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**Head**

**Abderrezak Bouchama, MD**

**Members**

- Mohammed Dehbi, PhD
- Taher Uz-Zaman, PhD
- Engin Baturcam, MSc
- Arslan Loualich, BSc
- Steve Bobis, DVM (part of the year)
- Mohamed Hassan, DVM (part of the year)
- Sahar Salem
- Ludivina Apilado, RN

**Collaborators**

- Corinne Kunzelmann, PhD
- Jean Marie Freyssinet, PhD
- Dominique DeProst, PhD
- Ayodele Alaiya, PhD
- Aaron Kwaasi, PhD
- Muhammad Chishti, PhD
- Ahmed Maqbool, PhD
- Abdelmoneim Eldali, MSc
- Wilhelmina Ventura

## RESEARCH PROJECTS

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**Project title: Effect of Xigris “Recombinant Activated Protein C” on Inflammatory and Haemostatic Responses in Primates Suffering from Lethal Heatstroke: Relation to Outcome. RAC# 2020 O17 – Phase 3**

**Investigators:** Abderrezak Bouchama, Mohammed Dehbi, Aaron Kwaasi, Abdelmoneim Eldali, Corinne Kunzelmann, Jean Marie Freyssinet and Dominique DeProst

### Project description

This project is supported in part by a Grant from Eli-Lilly, Indianapolis, USA. We aim to assess the effect of recombinant activated protein C (Xigris), an inhibitor of the coagulation system on the inflammatory response, organ functions and survival in baboons suffering from lethal heatstroke.

Fourteen animals were randomized to Xigris (n=7) given at 24 µg/kg/hr continuous infusion at the onset of heatstroke and compared with animals (n=7) treated with placebo. We examined the effect of Xigris on markers of organ injury/dysfunction, inflammatory and coagulation responses and animal outcome (survival versus mortality).

### Progress

Project completed and one manuscript was submitted for publication.

**Project title: Profiling of Heat Shock Proteins Expression in a Baboon Model of Heatstroke. RAC#**

**Investigators:** Abderrezak Bouchama, Mohammed Dehbi, Engin Baturcam, Arslan Loualich, Abdelmoneim Eldali, Aaron Kwaasi, Ahmed Maqbool and Mohammed Chishti.

### Project description

Heat shock proteins (referred to as molecular chaperones) represent a growing family of stress-inducible proteins. They act by helping in the refolding of misfolded proteins in response to various stresses including heat stress, and thus, they play key roles in maintaining cellular homeostasis and integrity during the exposure to a given stress. In this project, we investigated the expression

profile of 3 major heat shock proteins (Hsp-60, Hsp-70 and Hsp-72) in a baboon model of heatstroke and the possible relationships with outcome.

Animals were randomly divided into 3 groups: sham-heated group, moderate heatstroke group and severe heatstroke group. Tissue samples were obtained at immediate autopsy (non-survivors) and euthanasia at 72-h (survivors) and homogenized. Expression of Hsps was monitored by western blot on lysates prepared from various organs.

### Progress

Project was completed and one manuscript is in preparation. In addition, two abstracts were accepted/presented as posters in 2007 in Munich, Germany and Orlando, USA.

**Project title: Proteomic Profiling of an Experimental Baboon Model of Heatstroke**

**Investigators:** Abderrezak Bouchama, Mohammed Dehbi, Ayodele Alaiya, Mai Al-Mohanna,

### Project description

In this project, we applied the proteomic profiling technology to identify targets that are deregulated during severe heatstroke using our baboon model.

Animals were randomly divided into 3 groups: sham-heated group, moderate heatstroke group and severe heatstroke group. Tissue samples were obtained at immediate autopsy (non-survivors) and euthanasia at 72-h (survivors). Liver tissues were homogenized, proteins were separated on 2D-gel electrophoresis and stained. Data were processed with the appropriate software (Bio-Rad).

### Progress

Our analysis indicated a total of 38 polypeptides that are differentially expressed between sham and severe heatstroke groups out of the 38 polypeptides, 24 were easy to cut. Their identity by mass spectrometry is underway.

**Project title: Signaling Pathways Involved in Heatstroke Pathogenesis: Role of Toll-Like Receptor-4 (TLR-4). RAC# 2063 001**

**Investigators:** Mohammed Dehbi, Taher Uz-Zaman, Abderrezak Bouchama, Mohammed Dehbi, Engin Baturcam, Steve Bobis, Moahamed Hassan, Sahar Salem, Ludivina Apilado, Abdelmoneim Eldali and Wilhelmina Ventura.

In this project, we will be focusing on the molecular mechanisms governing the inflammatory, tissue injury and death responses associated with heatstroke using a mouse model. Our initial work is primarily emphasized on the role of TLR-4, a key component involved in various inflammatory responses such as sepsis, shock, burn, trauma, tissue injury and microbial infection, particularly to specific microbial components such as the endotoxin lipopolysaccharide (LPS). Our working hypothesis was based on the observation that heatstroke was associated with a release in the circulation of LPS. In addition, blocking the effects of LPS by administration of anti-lipopolysaccharide agent was shown to improve animal survival from heatstroke effects. These observations prompt us to raise the question as to whether LPS triggers or potentiates the inflammatory response observed in heatstroke cases. In an attempt to dissect this relationship, we took advantage of the availability of LPS-resistant C3H/HeJ mice, an inbred strain that resists the LPS effects due to a mutation in TLR-4. The wild type strain C3H/HeOuj is used as control.

For each strain, animals were randomly divided into 2 groups: sham-heated group, heatstroke group. Blood and tissue samples will be collected at the onset of heatstroke and at various time points during the recovery period. Expression profiling of a panel of pro-inflammatory and anti-inflammatory mediators will be monitored. Survival rate will be established.

### Progress

The project was initiated on August 2007. We successfully established the mouse model of heatstroke. We almost achieved the *in vivo* aspect of the project (induction of heatstroke in wild type and mutant as well as blood and organ samplings).

Based on our results we surprisingly and unexpectedly found that the integrated of TLR-4 is executed for resistance to heatstroke and mice carrying a mutation of in the cytoplasmic domain of TLR-4 are more vulnerable to heat stress than the wild type. We are still in the process of confirming these interesting findings.

In parallel, we successfully cloned the HMGB1 protein as well as fragment derived from HMGB1 as a recombinant protein with GST and HIS tags. A mid-scale protein purification was already done.

### FUTURE RESEARCH DIRECTIONS

1. Evaluating novel therapies using the primate models of heatstroke (KACST approved grant; 340,000 SAR for 2 years). This project is a direct extension of our strategic goals to unravel the mechanisms of tissue injury, organ failure and death in heatstroke. This project consists of a preclinical trial using novel inhibitors of tissue factor/Factor VII, 2 key targets involved in the coagulation cascade. We anticipate that successful molecules will form the basis for human trial. The project was postponed due to the discontinuation of active site inactivated FV a. The use of alternative molecule(s) is under investigation.
2. Brain injury in heatstroke: Study using diffusion MRI, MR-spectroscopy & PET in baboons (KACST approved grant; 1,500,000 SAR for 3 years). This project will emphasize on the early heatstroke-induced brain alterations in a real time. The project is expected to start soon as baboons become available.
3. Genomic and proteomic profiling of heatstroke in a mouse model (RAC approved project #2070 O15). The completion of genome sequence of various species and the recent development of numerous technologies such as microarrays, transcriptomics and proteomics profiling are providing the opportunity of discovering key targets for a wide range of diseases including heat injury. We hypothesize that the application of the expression profiling technology will help identifying one or multiple targets underlying heatstroke pathogenesis. Such targets will in turn be useful for the diagnosis of this disease, monitoring of its progression, understanding its underlying mechanisms and ultimately, developing innovative therapeutic/diagnostic approaches.
4. Investigating the molecular basis of resistance/sensitivity to heat stress in human volunteers using both genomic and proteomic profiling approaches (This project was approved to start in May 2008). We hypothesize that the application of functional genomics using gene expression profiling, both at

the level of transcriptomics and proteomics, will help to identify the molecular basis that underline the loss of tolerance to heat based on age and gender (i.e. the young, elderly male and female subjects).

## PUBLICATIONS

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- Bouchama A, Dehbi M, Mohamed G, Matthies F, Shoukri M, Menne B. Prognostic Factors in Heat Wave-Related Deaths: A Meta-analysis. *Arch Intern Med.* 2007 #167:2170-2176.
- Bouchama A, Dehbi M, Chaves-Carballo E. Cooling and hemodynamic management in heatstroke: practical recommendations. *Crit Care.* 2007 #11:R54.
- Bouchama A, Kwaasi A, Dehbi M, Al Mohanna F, Eldali A, El-Sayed R, Tbakhi A, Alzahrani AS, Roberts AG. Glucocorticoids do not protect against the lethal effects of experimental heatstroke in baboons. *Shock.* 2007 #27:578-583.

## Submitted

- Bouchama A, Kunzelmann C, Dehbi M, Kwaasi A, Eldali A, Zobairi F, Freyssinet JM, de Prost D. Recombinant human activated protein C attenuates endothelial injury and inhibits procoagulant microparticles release

in baboon heatstroke (Submitted to *Arteriosclerosis, Thrombosis & Vascular Biology*)

- Roberts G, Chishti M, Al-Mohanna F, El-Sayed R, Bouchama A. Microvascular injury, thrombosis & inflammation underlie the pathogenesis of heatstroke: A study in baboon (Accepted for publication *Arteriosclerosis, Thrombosis & Vascular Biology*)

## Presentations

- Bouchama, A. Ahmed M, Kwaasi A, Loualich A, Chishti M, Roberts G and Dehbi M. Circulating Hsp-72 is an early and long lasting marker of heatstroke severity. The 36th Critical Care Congress, Orlando, Florida, USA (February 17-21, 2007). Abstract published in *Critical Care Medicine* #34: A49.
- Dehbi M. Ahmed M, Kwaasi A, Loualich A, Chishti M, Roberts G, Al-Mohanna F and Bouchama, A. Expression profiling of heat shock proteins in a primate non-human baboon model of heatstroke. The 7<sup>th</sup> World Congress on Trauma, Shock, Inflammation and Sepsis, Munich, Germany (March 13-17, 2007).
- Bouchama A. 2<sup>nd</sup> International Pan-Arab Critical Care Medicine Congress, Dubai, UAE (Apr. 20-24, 2007).
- Bouchama A, Dehbi M, Mohamed G, Matthies F, Shoukri M, Menne B. Prognostic factors in heat wave-related deaths: A meta-analysis. The 7<sup>th</sup> IEA-EMR Scientific Meeting, Riyadh, KSA (November 27-29, 2007).

Core Facility

# LABORATORY ANIMAL FACILITY

The primary function of the Laboratory Animal Facility (LAF) is to assist investigators in their obligation to plan and conduct animal experiments in accord with the highest scientific, humane and ethical principles. This is achieved by development and maintenance of a comprehensive, high quality animal care program,

One of the main activities of the LAF is to maintain and provide purebred animal species for the research needs of scientists and physicians. The section maintains and breeds colonies of mice, rats, hamsters, guinea pigs, rabbits, dogs and baboons. The staff of the section ensures that newly procured animals are taken through strict quarantine procedures and remain healthy.

The Division of Lab Animal Facility provides high quality care, training scientists, technicians and students in the proper handling, care and use of animals in scientific research. , and provide consultation in the safe, humane use of laboratory animals in research and education in compliance with international regulations and KFSH policies.

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**Head**

**Ra'afat M. El Sayed, DVM, MVSc**

**Members**

- Falah H. Al-Mohanna, DVM, MSc
- Catalino L. Santos
- Mohammed Hassan, DVM (RC Grant)
- Merfat A. Elyan
- Julius D. Mabborang
- Wilfredo B. Antiquerra
- Rolando G. Monzaga
- Pio D. Oliveras
- Ruben C. Delos Santos
- Mona A. Saleh (RC Grant)
- Bahaa Salem (RC Grant)

## AVAILABLE FACILITIES

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### Animal Housing

Currently the facilities house the animals at the King Faisal Specialist Hospital and Research Centre at the:

- a. LAF (200 square meters) is located at the basement of the RC. Most of animal rooms were converted into laboratories.
- b. An outdoor new renovated dog kennel to house 36 individual dogs.
- c. Indoor Baboon quarantine, negative containment facility, this a renovated (91 square meters), has two controlled quarantine rooms to house 40-50 baboons during 90 days of quarantine time, procedure room, necropsy room, morgue room and cage washing room.
- d. Outdoor baboon cage (115 square meters) located behind Warehouse number 7. It is wire chain link fence structure with 8 rooms and a T-shaped corridor covered with canvas to provide shelter from the hot sun. Two desert coolers are used to provide needed comfort temperature during hot weather.
- e. Sheep shelter pen is located adjacent to the outdoor baboon house, has three sections, to house new arrival sheep.
- f. The CCC-LAF is a modern well equipped facility for receiving new small animals, holding, breeding and experimentation and containing 8 animal rooms to house the small laboratory animals such as mice, rats, hamsters, guinea pigs and rabbits. This beside bedding storage, food storage, cage & rack storage, washing area (dirty & clean side), procedure room, laboratory, lounge and offices.
- g. Surgical Theatre: includes scrub area for surgeons and surgery room, basic diagnostic lab for animal (hematology, basic chemistry analyzer, coagulation, blood gas,).
- h. Microsurgery Animal Lab
- i. Laparoscopy Training Animal Lab
- j. Animal physiology & pharmacology lab.

### Service Work

- a. Responsible for maintenance, procurement and breeding of a variety of common laboratory animals used in biomedical research and teaching.
- b. Provide quality services to maintain healthy animals and intervene in control of diseases, diagnosis and

treatment of sick animals.

- c. Enforce professional and international standards set for Laboratory Animal Science practice of providing valuable assistance and advice to physicians and scientists using laboratory animals.
- d. Provide technical support to physicians, researchers and technicians to carry out animal related work.
- e. Prepare for the accreditation by the American Association for the Accreditation of Laboratory Animal Care International. Preparations are in progress for this endeavor and achieving the accreditation will both attract and facilitate obtaining research grants and contracts. Moreover, it will add prestige to our Research Centre.
- f. Breeding and maintain nude, scid, diabetic, transgenic and knock-out mice.
- g. Production of monoclonal antibodies for diagnostic and therapeutic applications.
- h. Use of human, animal tumor models for therapeutic investigations.
- i. Special instrumentation of rodents for cardiovascular and hypertension research (Telemetry new technology).
- j. Biosafety facilities for experimentation with infectious and hazardous agents.
- k. Cardiovascular experimentation in large animals

## CORE ACTIVITIES

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Staff at LAF unit assist and/or collaborate with researchers of KFSH & RC as well as national and international scientists by providing the following services:

- a. Advising on the selection and procurement of the appropriate animals for experiments.
- b. Maintaining and providing appropriate animals to various investigators.
- c. Training animal users with emphasis on proper handling and care of laboratory animals.
- d. Weekly or on demand, the Animal Facility staff provides blood and tissue samples from laboratory animal to the Pathology, Microbiology and RC.
- e. Pre and post-surgical cares
- f. Housing animals in accordance with the Standard Operating Procedure (SOP).
- g. Veterinary care such as disease prevention, treatment and vaccination.
- h. Coordinate & manage with the Pest Control

Section for the euthanasia of harmful and trapped animals.

## RESEARCH PROJECTS

The LAF is actively involved in providing laboratory animals and/or collaborating with several investigators at KFSH&RC as summarized below.

### In-house Research Projects

- a. RAC#2063 013. Signaling Pathways Involved in Heatstroke Pathogenesis.
- b. RAC# 2050 012. Coagulation & Fibrinolysis Response Patterns to Severe Heatstroke & Its Relation to Inflammation & Cell Injury in Baboon Model: Effect of Tissue Factors Neutralization on Outcome
- c. RAC# 2020 017 Phase III. Effect of Recombinant Activated Protein C on Inflammatory & Hemostatic Responses in Primates From Lethal Heatstroke: Relation to Outcome
- d. RAC# 2020 017 Phase II. Treatment of Heatstroke With Glucocorticoids: A Study in Baboons
- e. RAC# 2060 003. Brain Injury in Heatstroke: Study Using Diffusion MRI, MR-Spectroscopy & PET in Experimental Baboon
- f. RAC# 2060 039. Modulating the Hypoxia Inducible Factor Signaling Pathways as a Therapeutic Modality to Regulate Neovascularization Related Retinopathies in Mice.

### Collaborative Research Project

- a. RAC# 2011 036. Testing the Effectiveness of a Prototype Vaccine Against Rheumatic Heart Disease in Baboon. Dr. L. Mammo, Dept. of Biological & Medical Research
- b. RAC#2060 007. Metabolic Syndrome, Diabetes & Cognitive Decline: Effect of Dietary Components on Insulin Resistance, Hyperlipidemia, Inflammation and Cognition in a Rodent Model. Dr. K. Collison, Dept. of Biological & Medical Research
- c. RAC# 2020 025. Cellular & Molecular Mechanisms in Cardiac Failure Using a Reversible Ovine Model. Drs. M. Qutainah & F. Al-Mohanna, Dept. of Biological & Medical Research
- d. RAC#2070 004. Role of P13-Kinase-AKT Pathway in Epithelial Carcinoma *In Vivo* Study (Nude /Scid mice). Dr.Khawla Al Kuraya, KFNC&R

### Supported Research Projects (provided animals):

- a. RAC#2050 046. *Vaccinia* Virus Complement Control Protein: Potential to Prevent Damage to Xenoreactive Cells in Rats. Dr. K. Collison, Dept. of Biological & Medical Research
- b. RAC# 2040 027. Synthesis of Different Radiofluorinated Precursors for Rapid Production of New PET Radiopharmaceuticals. Dr. I. Al Jammaz, Dept. of Biomedical Physics
- c. RAC# 2042 001. Production of 'Cold Kits' for Technitium-99m Radiopharmaceuticals. Dr. I. Al Jammaz, Dept. of Biomedical Physics
- d. RAC# 2020 002. Photo Biostimulation: Laser Effect in Wound Healing of Diabetic & Non Diabetic Rats. Dr. F. Al Watban, Dept. of Biological & Medical Research
- e. RAC# 2030 057. Gene Therapy for Anaplastic Thyroid Carcinoma with a Single Chain Interleukin 12 Fusion Protein *In Vivo* study. Dr. Y. Shi, Dept. of Genetics
- f. RAC# 2030 057. Investigation of BRAF Mutation in Thyroid Carcinoma from Saudi Population in Mice. Dr. Y. Shi, Dept. of Genetics
- g. RAC# 2050 048. Identification of Genes Involved in Thyroid Cancer Metastasis by Microsurgery Analysis of Thyroid Carcinoma Cell Line with High Metastasis Potential. Dr. Y. Shi, Dept. of Genetics
- h. RAC# 2020 001. Study of Photodynamic Therapy with Laser Wounds for Determination of Efficiency in Optimum Dosimetry & Its Limitations. Dr. F. Al Watban, Dept. of Biological & Medical Research

### Assistance Provided to Investigators:

- a. RAC# 2031 088. 10 Baboons. P.I. Dr. Chandra Mullangi
  - . 34 ECG
  - . 60 CBC, cardiac enzymes, 80 ml blood
  - . 10 Echo
  - . 5 PET/MRI/SPECT
  - . 2 Autopsy
- b. RAC# 2031 019. 10 Dogs. P.I. Dr. Majid Fayyadh
  - . 7 Cardiac surgery
  - . 14 ECG
- c. RAC# 2011 036. P.I. Dr. Layla Mammo
  - . 320 CBC, ESRC, Enzymes
  - . 320 Blood cultures
  - . 320 Throat swabs
  - . 320 Vital signs
  - . 160 Echo

- . 300 ECG
- . 20 Baboons autopsied and tissues (heart, valves, lung, liver, muscles, skin, kidney and brain) were collected, evaluated and preserved for histopathology

and the Riyadh Zoo. These collaborations consist of providing samples of animal blood and tissue for various procedures as needed by investigators, providing stocks of various laboratory animals and offering veterinary assistance and technical services.

## COLLABORATION

In addition to our major activity at the level of KFSH&RC, our unit collaborates with other national institutions such as: Ministry of Agriculture, King Saud University, National Commission for Wildlife Conservation and Development

## FACTS AND FIGURES

In 2007, LAF assisted research and training activities by providing various animals ranging from rodents to primates:

	Mice	Mice Nude	Mice SCID	Transgenic	Rats	Rabbits	Hamster	Guinea pigs	Dogs	Sheep	Baboons
<b>Used</b>	685	191	48	X	369	X	X	50	25	17	30
<b>Inventory</b>	584	251	51	93	492	15	22	53	46	2	62

## Rats and Mice Census

Mice		Transgenic Mice		Rats	
Strains	N	Strains	N	Strains	N
BALB/C	150	Rho-VEGF	48	Rat,S.D.	337
CBA/J	40	J49 Rxb	3	Wistar	70
C3H/HeJ	53	FLP	3	Long Evans	67
C3H/HEOUJ	100	TEA J49 Rxb	2	Fisher F344/NTAC	18
C57BL/6J	124	5 -/-(129)	5		
C57BL/6 ADRAZA	70	CMV-cre	4		
C3H/HcouJ-Trp53		J49 -/-	4		
SCID MICE	51	ROR	2		
NUDE MICE NU/J	251	Rxb 129	4		
NOD/MvkTac	47	TEA Rxb	5		
		HYK 1	5		
		TEA j49(DKO)	4		
		HYK1 Rxb	4		
<b>TOTAL</b>	<b>886</b>	<b>TOTAL</b>	<b>13</b>	<b>TOTAL</b>	<b>492</b>

## TRAINING AND EDUCATIONAL ACTIVITIES

### Assisted Saudi students in research programs for MSc and PhD:

#### Achievements in 2007

- Renovation and upgrade of Non-Human Primate Facility (Baboon Center).
- Build up a new Dog Kennel to house 36 dogs and a back yard for exercising.
- Establishment of Biosafety Facilities for

experimentation with infectious and hazardous agents.

- Establishment basic veterinary diagnostic lab.
- Establishment of Telemetry new technology for cardiovascular, hypertension and heatstroke research in rodent.
- Establishment of small animal procedure room at CCC-LAF designed for multi-purpose use including routine experimental procedures and performance of aseptic surgery

Training Program	Animals Used	Training Period
Assisted Ms Najla Al Abdulsalam, MS student from King Faisal University, Hofouf for her MSc Project: Effect of Dexamethasone on Pregnancy Outcome & Development of the liver in SD Rats	SD Rats (250 Rats)	from June 2007 – to present
Assisted Ms Mouna Al-Amoudi from Physiology Department, Girls College, Riyadh on her PhD Project: A Correlation Study Between Low Protein Diet and The Renal Hypertensive Injury in rats	Hypertensive Rats	08 September 2007 – to present
Provided basic surgery training to Ms Julie Carscdden	Small & large animal	15-28 June 2007
Provided one month summer training for 5 male high school students of Ibn Sena Program, King Abdulaziz and his Companion Foundation for the Gifted.	Mice/Rats	29 June – 28 July 2007 (1 month)

## FUTURE PLANS

- A training course should be offered to the staff of the current Laboratory Animal Facility. This course will also be available to the staff of other similar institutions in Riyadh. A considerable amount of educational material should be available in the form of interactive computer programs, videos, slides and manuals.
- Training scientists, technicians and students in the proper handling, care and use of animals in scientific research.
- An educational departmental library should be started to collect the aforementioned materials and books related to Laboratory Animal Science.



## Research Unit

# TUBERCULOSIS

According to estimated given by the World Health Organization (WHO), *Mycobacterium tuberculosis* (MTB) kills 3 million people per annum and there are 8 million new cases each year. One third of the world's population is infected with MTB and a new person is infected each second. Tuberculosis (TB) is a major health problem in Saudi Arabia and humans as well as animals are infected. The incidence of TB in animals is not known and no efforts have been made in this area to date. In humans the incidence varies from one region to another and reports on incidence rate of TB in Saudi Arabia give a contradictory picture. In Jeddah for instance reports show that the incidence rate is 64 per 100,000. On the other hand in Riyadh the incidence rate is 32 per 100,000(1). Reports on anti-tuberculosis drug resistance from different regions of Saudi Arabia give a contradictory picture of the status of drug-resistant TB in the country too. As a result TB is the only infectious disease which has not been brought under control in this country. Our unit is focusing on the disease attempting to provide research based information to authorities to enable them to draw strategies to control the disease.

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### Head

Sahal Al-Hajaj, PhD

### Members

Viqaruddin Khaja Mohammed,

MSc (part of the year)

Maryam Al-Nasser

(part of the year)

Ohoud Al-Hajri

(part of the year)

## RESEARCH PROJECTS

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### **Project title: Fingerprinting of Mono and Multi-Drug Resistant TB**

**Investigators:** Sahal Al-Hajoj, PhD, Fahad Al-Rabiah, MD, Sahar Al-Thwadi, MD

#### **Project description**

This project is a direct extension of the work that was started in 2003. In this project, we emphasized on the mechanisms leading to the spread of multi-drug resistant TB. More specifically, we examined whether there are certain strains that are causing the drug resistance, and if so, what is their prevalence, their location across the country, their antibiotic resistance profile and finally, the proportion of imported strains.

#### **Progress**

Project completed and one manuscript is in preparation.

### **Project title: Molecular Basis of Drug Resistant Tuberculosis in Saudi Arabia**

**Investigators:** Fahad Al-Rabiah, MD, Sahal Al-Hajoj, PhD, Sahar Al-Thawadi, MD

#### **Project description**

The main goal of this project is to extensively evaluate the efficacy of the recently implemented Direct Observed Therapy (DOTS) control program of tuberculosis in Saudi Arabia, and its relationship to other developed countries. This will be accomplished through (a) the molecular analysis of the emergent patterns of drug resistance and, (b) the determination of the rate of transmission versus acquisition of drug resistance, by combining genotyping data with clinical data. To achieve this goal, we propose to identify in Saudi Arabia the frequencies of gene mutations associated with drug-resistance and the distribution of multi-locus Variable Number Tandem Repeat (VNTR) genotypes of drug-resistant strains, based on a national collection of mycobacterium tuberculosis. Obtained results will facilitate the development of a national database in a generalized standard format as a new tool for the adaptation of strategies for controlling the dissemination of Multi-drug resistant TB (MDR-TB) strains in the country. This project will be a cornerstone,

and serve as the basis for the institution of a National Reference Center.

#### **Progress**

More than 300 isolates have been collected from all over the country. Our preliminary analysis indicated that these strains are mono and multi-drug resistances. Work is still ongoing.

### **Project title: Epidemiology of Drug Resistance TB in Saudi Arabia (KACST approved grant).**

**Investigators:** Sahal Al-Hajoj, PhD, Fahad Al-Rabiah, MD, Abdullah Al-Drees

#### **Project description**

The purpose of this project is to study the drug resistance level in the country.

#### **Progress**

Preparation is underway to start this project.

### **Project title: Detection of Interferon Gamma Production for the Diagnosis of Latent Tuberculosis in Patients for Kidney Transplantation. RAC# 2070 013**

**Investigators:** Sahal Al-Hajoj, PhD, Abdulrahman A. Alrajhi, MD, Fahad Al-Rabiah, MD, Ashraf Ali Mohammad Atia, MD

#### **Project description**

Latent tuberculosis infection is prevalent in Saudi Arabia, and more specifically, the end-stage renal disease patients. Kidney transplantation related immune suppression is a potent risk factor for activating latent tuberculosis. The current pre-transplant protocols mandate active search for latent tuberculosis in all eligible end-stage renal disease patients. Latent tuberculosis is now being screened to be used in clinical assessment, tuberculin skin test, and chest radiography. Chemoprophylaxis is effective in preventing tuberculosis reactivation. New tools based on measuring gamma interferon production by lymphocytes in response to Mycobacterium tuberculosis specific antigens are now licensed to diagnose latent tuberculosis in various populations. Data from immunocompromised hosts or pre-transplant patients are scarce. The utility of one of these tests is assessed in this study. Quantiferon®-TB

Gold test is used prospectively in this study in patients with end-stage renal disease before undergoing kidney transplantation. The aim of the study is to evaluate the utility of Quantiferon®-TB Gold test for diagnosing latent tuberculosis infection in patients planned for kidney transplantation. Over three years, 300 patients will be enrolled in this observational, non-interventional study. The utility of this test will be assessed in comparison of the current available tools. The hope is that this new test will enhance our ability to diagnose latent tuberculosis and prevent active disease in similar immune suppressed patients.

### Progress

This project has been finally approved by Research Advisory Council (RAC) and preparation is underway to start this project.

### FUTURE RESEARCH DIRECTION

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We are hoping to put together the data generated over the last 4 years to build a proper data base for all types/clades of TB present in Saudi Arabia together with the epidemiological data and their drug resistance profile. This data base should be available for all health authorities to enable them to tackle the problem based on such solid data.

### International Collaboration

1. Dr. Dick vanSoolingen, Netherlands, National Institute of Public Health and the Environment.
2. Dr. Philip Supply, France, Institute of Pasteur de Lille
3. Dr. Christophe Sola, and Nalin Rostagi from Guadeloupe, Institut of Pasteur de Guadeloupe.
4. Dr. Timothy McHugh, UK, Department of Medical Microbiology, Royal Free University College Medical School, London.

### PUBLICATIONS

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- Al-Hajj SA, Zozio T, Al-Rabiah F, Mohammad V, Al-Nasser M, Sola C, Rastogi N. A First Insight on the Population Structure of *Mycobacterium Tuberculosis* in Saudi Arabia. *J Clin Microbiol.* 2007 Aug;45(8):2467-73.
- Al-Hajj SA, Al-Rabiah F. Is Saudi Arabia a Fertile Land for Exchanging Infectious Diseases? *Saudi Med J.* 2007 May;28(5):803-4.
- Al-Hajj SA, Mohammed VK, Al-Hokail AA. Usefulness of Molecular Techniques to Identify Ongoing Tuberculosis Transmission in Saudi Arabia. *Saudi Med J.* 2007 Feb;28(2):268-270.



# **CYCLOTRON AND RADIOPHARMACEUTICALS**



The Department of

# CYCLOTRON AND RADIOPHARMACEUTICALS

*C*yclotron and Radiopharmaceuticals Department performs two distinct functions in the Research Center: Radiopharmaceuticals manufacturing; and Radiotracer Research.

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*Chairman*

**Manhar M. Vora, PhD**

---

*Deputy Chairman*

**Ibrahim Al-Jammaz, PhD**

---

*Administrative Support Staff*

Jhonna L. Canicosa

Nora B. D'Souza

## RADIOPHARMACEUTICAL MANUFACTURING

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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. Cyclotron and Radiopharmaceuticals Department is the only facility of this kind within the geographical region manufacturing these specialty products. Moreover, C&R Department within the Research Center has been manufacturing several different cyclotron-based radiopharmaceuticals (diagnostics) for over two decades, and has recently added therapeutic products derived from reactor-based isotopes. 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). The PET radiopharmaceuticals are manufactured in compliance with international standard of quality, reliably facilitating the PET/CT investigations for cancer patient management.

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 9001:2000 Quality Management System for further quality enhancement.

## RADIOTRACER RESEARCH

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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 2007

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**Radiopharmaceutical manufacturing:** In the Year 2007, C&R Department's production section continued to manufacture and supply radiopharmaceutical products conforming to international standard of purity, efficacy and safety. Product quality was maintained through strict adherence to the international guidelines of Good Manufacturing Practices (GMP) and the ISO 9001:2000 Quality Management System. Due to continued technical problems with the aging cyclotron, volume of production remained relatively unsatisfactory. However, the maintenance work was nearly completed by end of the year. Products distribution to the user centers remained at less than the traditional level, with considerable decrease in both, volume of production and the revenues. On the other hand, operation of the RDS cyclotron resulted in reliable and high volume production of PET radiopharmaceuticals.

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). Several expert and consultation missions were assigned to the senior staff in the C&R Department to share their experience with developing countries in the Western Asia region and beyond. Also, a senior scientist has been appointed to co-author a number of manuals in book format for benefit of the cyclotron isotopes manufacturers.

**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. Specific attention was focused on establishing a Molecular Imaging facility to take advantage of KFSH&RC's commending position in resources availability and PET imaging.

## HIGHLIGHTS OF THE ACCOMPLISHMENTS FOR THE YEAR 2007

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### Radiopharmaceuticals Production Related

- 12,001 units of radiopharmaceuticals distribution to 40 nuclear imaging centers in the Kingdom and abroad

- 6,427,439 in revenues from distribution of radiopharmaceuticals
- 98.3% process success rate in manufacturing radiopharmaceutical products
- Achieved objectives of the ISO 9001:2000 Quality Management System, including customer satisfaction rate of 91.9%
- Zero non-conformities: ISO 9001:2000 Quality Management recertification
- International Atomic Energy Agency (IAEA) activities:
  - Participation in a research project to improve isotopes production rate in a cyclotron
  - A senior scientist appointed as a Consultant for Establishing Quality Assurance and Good Manufacturing Practices of Medical Radioisotopes and Radiopharmaceuticals in Syria
  - A senior scientist appointed to co-author four Guidebooks pertaining to manufacturing cyclotron isotopes and radiopharmaceuticals

#### **Radiotracer Research Related**

- 8 active research projects
- 6 Grant funds (KACST funded, over 3-4 years)
- 4 publications in peer-reviewed journals
- 12 abstracts and presentations

#### **FUTURE DIRECTIONS**

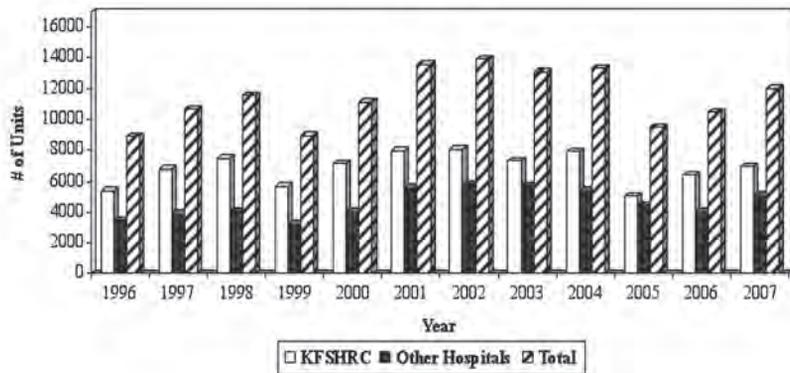
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With an ultimate aim of becoming a single source of all radiopharmaceutical needs of the Kingdom, an ambitious project entailing physical expansion of the C&R Department has been initiated. Upon completion of this project, perhaps in year 2009, we expect to achieve our ultimate objective of self-reliance and capacity building for the Nation. Project entails:

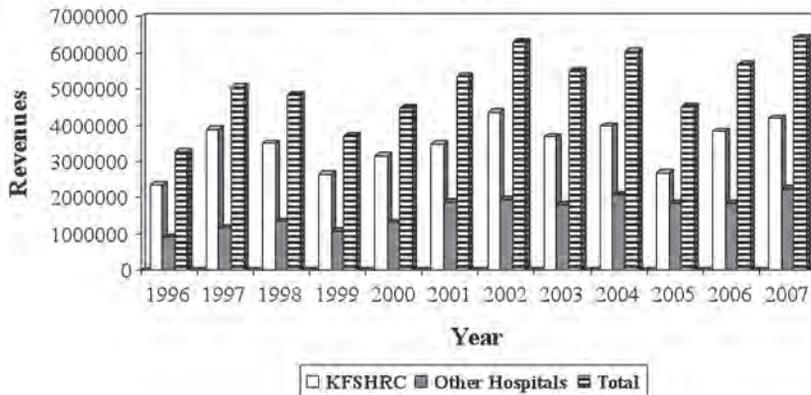
- Augmentation of the aging cyclotron with a state-of-the-art 30 MeV medium energy medical cyclotron
- Installation of Technetium-99m Generators manufacturing plant
- Construction of Phase II of the Cyclotron Expansion building

In summary, in the Year 2007, Radiopharmaceuticals production activity maintained its course with slight increase in units distribution and revenues. The most notably accomplishment in research was the seed project for establishing a molecular imaging program.

**Total Number of Units Distributed  
(1996 – 2007)**



**Total Revenues  
(1996 – 2007)**



## The Section of

# RADIOPHARMACEUTICAL RESEARCH

The utilization of nuclear molecular imaging will be sustained by developing novel, selective and sensitive radiotracers based on proven physiological, biochemical and pharmacological concepts. For this reason our research has focused on radiolabeling bioactive molecules such as peptides, peptidomimetics and drugs, and to explore their potential application as diagnostic or therapeutic radiopharmaceuticals. Ideally these target molecules must be labeled with isotopes of natural elements such as C-11, N-13 or O-15. However, the short half-lives of these isotopes place limitations on their application. Nonetheless F-18 has been an excellent substitute for these elements. The replacement of a hydrogen or hydroxyl by F-18 in some cases has resulted in better radiotracers. These investigations require the development of efficient, fast and simple chemical reactions, optimizing analytical methods and techniques for the product and finally performing the requisite *in vitro* and *in vivo* tests including imaging to prove their eventual utility in humans.

Radiohalogenated peptides and drug molecules are potential radiotracers targeting a gamut of diseases including cancer, infection and inflammation, apoptosis, tissue and organ rejection, diabetes, etc. Additionally, the kinetics of most ligand-receptor interactions favors radiolabeling with Tc-99m and other short-lived radionuclides such as Cu-64.

Increasing demand for nuclear medicine imaging procedures implies that old methods must be improved and new ones sought for the production of radionuclides and radiopharmaceuticals. Initial effort to produce and evaluate other radionuclides will be undertaken in the near future.

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### **Head**

**Amartey John K, PhD**

### **Members**

Al-Jammaz Ibrahim, PhD

Okarvi Subhani M, PhD

Al-Qahtani Mohammed, PhD

Al-Otaibi Basem, MSc

Carroll Edward, BS (Eng.)

Esguerra Celestina, BSc

## RESEARCH PROJECTS

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**Project title:** Synthesis of radiofluorinated precursors for rapid production of new PET radiopharmaceuticals. (RAC # 2040-027).

**Principal Investigator:** Al Jammaz, I; **Col:** Amartey JK

### Project description

- To develop variety of benzene (hydrophobic) and pyridine (hydrophilic) fluorinated substrates in a fast way.
- To radiofluorinate bioactive molecules and perform in-vitro and in-vivo characterization to determine their potentiality as imaging agents.

### Progress

- The non-radioactive and radioactive N-succinimidyl-4-fluoronicotinate, isonicotinate (SFP) and fluorobenzoyl hydrazide (FBH) were prepared and characterized.
- SFP and FBH were successfully coupled to folate hydrazide and N-succinimidyl activated folate respectively.

**Project title:** Preparation and Characterization of Radiolabeled Bombesin Peptide Analogs Targeting Human Cancers: A Foundation stone for Molecular Imaging program (KACST #AT 25-06, RAC# 2030-058).

**Principal Investigator:** Al-Jammaz I; Okarvi SM; **Cols:** Bin Amer S; Amartey JK.

### Project description

- To synthesize analogs of bombesin (BBN) peptide containing critical receptor binding sequence but different spacer group between the peptide and the chelating sequence
- To radiolabel these peptides with Tc-99m (SPECT) and F-18 (PET)
- To study in vitro and in vivo characteristics of the radiolabeled peptides using BBN receptor-positive cell lines (e.g. PC-3 and MCF-7).

### Progress

- A number of BBN peptide analogs have been synthesized containing different spacer groups.
- Initial experiments of radiolabeling BBN peptide analogs with Tc-99m was achieved by the ligand exchange method in the presence of stannous tartrate.
- Coupling of prosthetic groups with BBN peptides is partially completed
- Radiolabeling of BBN peptides with F-18 is in progress.
- After radiolabeling, purification and isolation of the desired radiolabeled peptides, in vitro cell-binding characteristics and internalization into breast cancer cells and in vivo experiments of Tc-99m/F-18-labeled BBN conjugates will be performed

**Project title:** Standardized High Current Liquid and Gas Targets for Cyclotron Production of Diagnostic and Therapeutic Radiopharmaceuticals" (IAEA# SAU13483, RAC# 2050 027).

**Principal Investigator:** Al Jammaz I.; **Cols:** Miliebari S., AlYanbawi S., Rahma S., Van-Heerden W.

### Project description

To increase production yields, specific activity, chemical purity and availability of F-18, N-13, Kr-81 and I-123 radiopharmaceuticals that are used in nuclear medicine by improving the following:

- beam current irradiation
- diagnostic tool for target monitoring during irradiation
- more understanding of in-target chemistry and
- recovery and characterization of a very expensive enriched material.

### Progress

- Different degraders (aluminum and graphite) were fabricated and tested on F-18 targets.
- Beam current was elevated to 38 $\mu$ A without blowing off or damaging degraders. This resulted in better F-18 yield, higher specific activity, less Radiation exposure and reliability of FDG production.

**Project title:** Brain Injury in Heat Stroke: Study Using Diffusion MRI, MR-Spectroscopy and PET in Experimental Baboon (RAC # 2060003, KACST AT-26-42).

**Principal Investigator:** Abderrezak Bouchama, **Co-I:** Mohammed Al-Gahtani

#### Project description

On an experimental non-human primate model of moderate and severe heatstroke that closely replicates human heatstroke, particularly the brain injury. The use of new neuron-imaging techniques such as Diffusion-weighted Magnetic resonance imaging (DWMRI), Magnetic resonance spectroscopy (MRS), and (PET) to experimental baboon as follows:

- Test the hypothesis that neurologic injury of heat stroke is due to cerebral ischemia.
- If so, identify susceptible brain regions to ischemia and their time-course until recovery or infraction.
- Investigate whether cellular energy metabolism, cell membranes and neuronal integrity, and inflammation are associated with heatstroke related brain damage;
- And finally correlate the findings with neurologic outcome and mortality.

Answering these basic questions may add to our understanding, and thereby might help formulate future neuroprotective strategies in heat stroke.

Progress: To commence in 2008.

**Project title:** Synthesis and Initial Evaluation of [18F]-VEGFR-2 Antagonist as a Potential Tracer Targeting Angiogenesis (RAC# 2070-011).

**Principal Investigator:** John K. Amartey

#### Project description

- To synthesize and perform initial in vitro evaluation of a potential angiogenesis imaging agent based on a quinalzoline pharmacophore.

#### Progress

- The synthesis of some key intermediate molecules has been completed.

**Project title:** Evaluation of radioiodinated laminin-1 derived peptide antagonist that blocks angiogenesis and tumor growth (RAC# 2060-001).

**Principal Investigator:** Mohammed H. Al-Gahtani; **Co-I:** John K. Amartey

#### Project description

- Radioiodinate the peptide (C8G) applying the direct electrophilic method.
- Perform radioligand binding experiments on activated HUVEC cells.

#### Progress

Radioiodination of the peptide and the positive control peptide (echistatin) has been completed

#### FUTURE RESEARCH DIRECTION

The results obtained so far on these projects are encouraging. In the development of the prosthetic groups for radiohalogenation we have successfully prepared compounds labeled with either [18F] or [123/125/131I]. These have been attached to selected molecules with moderate to high labeling efficiencies. With this technique in hand we are in a position to radiohalogenate specific biomolecules targeting cancer, infection and inflammation, etc. Biological evaluations of some of the promising radiotracers are ongoing to fully establish their utility, especially with recent acquisition of a small animal imager. Additionally, we continue to explore methods that are high-yielding, robust, and reproducible and also reduce the radiohalogenation reaction times.

Bifunctional derived radiometal chelating experiments with Tc-99m and other radiometals shall be pursued. In nuclear and radiochemistry the next area of investigation to increase yield would be target re-design and better electroplating to improve cooling during irradiation. Therefore we intend to continue to intensify our efforts in these areas and to develop and produce other short-lived radionuclides to further our overall goals.

## PUBLICATIONS (2007)

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- S. M. Okarvi: Peptide-based radiopharmaceuticals and cytotoxic conjugates: Potential tools against cancer. *Cancer Treatment Reviews*. 34: 13-26 (2008).
- S. M. Okarvi: Evaluation of radiolabeled bombesin analogs in animals (Letter to the Editor). *Breast Cancer Research Treatment*. 108(1):151 (2008).
- I. Al Jammaz, S. Al-Yanbawi, S. Melibari, and S. Rahma, Standardized High Current Solid Tellurium-124 Target for Cyclotron Production of Iodine-123/124 Radionuclides, *Radiochem. Acta.*, 95, 11, 2007.
- I. Al Jammaz, B. Al-Otaibi and J. Amartey, Rapid method for radiofluorination of pyridine derivatives: prosthetic groups for radiolabeling bioactive molecules, International Atomic Agency proceeding 11, 2007.
- I. Al-Jammaz. Oral presentation on Cyclotron Based Radiopharmaceuticals: Production and Research and Development, IAEA Scientific Visit, Budapest University, Hungary, May, 2007.
- I. Al-Jammaz. Oral presentation on Rapid Method for Radiofluorination of pyridine derivatives: prosthetic groups for radiolabeling bioactive molecules, IAEA Scientific Visit, Budapest University, Hungary, May, 2007.
- I. Al-Jammaz. Oral presentation on Production and quality control of cyclotron radiopharmaceuticals, Monrol Ltd., IAEA Scientific Visit, Istanbul, Turkey, May, 2007.
- I. Al-Jammaz. Oral presentation on Standards of Practice Specific to PET Radiopharmaceutical, IAEA Regional Meeting, Seoul, Korea, July, 2007.
- I. Al-Jammaz. Oral presentation on The Future of PET Radiopharmaceutical, IAEA Regional Meeting, Seoul, Korea, July, 2007.
- I. Al-Jammaz. Oral presentation on cyclotron radiopharmaceuticals, Syrian Atomic Energy Commission, IAEA Expert Visit, Damascus, Syria, October, 2007.
- I. Al-Jammaz. Oral presentation on PET Radiopharmaceutical Research & Development Syrian Atomic Energy Commission, IAEA Expert Visit, Damascus, Syria, October, 2007.
- S. M. Okarvi: Preparation, labeling and evaluation of a hybrid peptide derived from tumor antigens for breast cancer imaging. *J. Nucl. Med.* 48: 304P (2007).

## Abstracts and Presentations

- I. Al-Jammaz: Oral presentations on, Production and Quality Control of Radiopharmaceuticals in Saudi Arabia, IAEA Regional Meeting, Shanghai, China, April, 2007.
- I. Al-Jammaz. Oral presentations on Bombesin Peptides: Potential Molecular Nuclear Imaging Probes Research Centre Annual Report, March, 2007.
- I. Al-Jammaz. Oral presentation on GMP of Radiopharmaceuticals in: The Status and Prospects IAEA Regional Meeting, Shanghai, China, April, 2007.

# GENETICS



## The Department of

# GENETICS

Whilst the mission, goals and objectives of the Department of Genetics remained the same during the 2007 calendar year, substantial changes in the structure and staffing of the Department were undertaken towards the achievement of these. Most significantly "Program" based research activities were developed further and are now firmly entrenched in the department. Current programs of the department address the study of Hereditary Deafness, Hereditary Vision Impairment, Developmental Genetics, Movement Disorders, Hereditary Immunology, Gene Therapy, Mendelian and Polygenic Cardiovascular Diseases, Cognitive Genetics, Inborn Errors of Metabolism, Mental Retardation and Nephrogenetics. During 2007 consolidation of the activities of ADL and the Department of Genetics were implemented resulting in single core/service facilities for sequencing, high density genotyping, Diagnostic Molecular Genetics and Animal Genetics. Establishment of these research and service units have both resulted in to some extent and facilitated externally funded grants such as that for Hereditary Deafness from the Prince Salman Centre for Disability Research and for Hereditary Mental Retardation and Microcephaly from the DHFMR. In addition sections of the department have attracted fully funded fellowships and collaborative research opportunities with entities such as Autism speaks. The research activities of the department are elaborated in specific abstracts that form part of the 2007 annual report. The translational nature of some of this work is evident through the commercial registration of Saudi Diagnostic Laboratories and the provision of molecular genetic testing at KFSH&RC through the ICIS network. Informatics challenges that are a consequence of the above achievements were addressed in 2007 and are a clear objective in respect of promoting research and service activities of the Department of Genetics in 2008.

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*Chairman*

**Brian Meyer, PhD**



## Research Unit

# GENE THERAPY

*G*ene 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 every front. We demonstrated that IL-12 induced cannabinoid receptor 2 (CB2) expression, which could be used as a target for future therapeutic intervention. We investigated BRAF mutation and its pseudogene activation in thyroid tumors from Saudi population. BRAF V600E mutation and its pseudogene activation were detected in more than 40% papillary thyroid carcinomas. We also conducted a genetic study of a Saudi family with familial primary cortisol resistance. We demonstrated for the first time that a homozygous G679S mutation of the GR- $\alpha$  gene is associated with severe cortisol resistance, whereas a heterozygous mutation of the same gene can lead to subclinical cortisol resistance. The effect of the heterozygous mutation was abolished in subjects carrying the ER22/23EK polymorphism.

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### *Head*

Yufei Shi, PhD

## RESEARCH PROJECTS

### Project title: IL-12 Gene Therapy Of Anaplastic Thyroid Carcinoma (Rac #2030057)

**Investigators:** Yufei Shi, Ali Al-zahrani , Ranjit S. Parhar, Minjing Zou

#### Project description

The incidence of thyroid cancer in Saudi Arabia is higher than that in the US. Based on the Cancer Incidence Report 1997-1998, National Cancer Registry, Ministry of Health, Kingdom of Saudi Arabia, the five most common cancers among 5231 female Saudi patients are breast (19.8%), thyroid (9.5%), leukemia (6.3%), NHL (6.1), and ovary (4.5%). In the US, however, the incidence of thyroid cancer is only 2% and is the eighth of the most common cancers (Cancer facts and figures 2002, American Cancer Society). Anaplastic thyroid carcinoma is the most aggressive type of thyroid malignancies with a mean survival time of less than 8 months. No effective therapeutic approach is currently available, making the development of novel treatments necessary. Interleukin 12 (IL-12) is a proinflammatory heterodimeric cytokine with strong antitumor activity. In the present study, we investigated the potential of IL-12 gene therapy for anaplastic thyroid carcinoma in BALB/c (nu/nu) nude mice.

#### Progress

Previously, we demonstrated that tumorigenicity of anaplastic thyroid carcinoma cell line ARO was significantly reduced following interleukin 12 (IL-12) gene transfer in nude mice. We suspected that tumor target structure in ARO/IL-12 cells might be changed as a result of IL-12 expression and such a change may make them more susceptible to be killed through mechanisms apart from NK-dependent pathway (Human Gene Therapy, 14, 1741, 2003). To identify genes involved in the change of tumor target structure in ARO/IL-12 cells, we examined gene expression profile of ARO and ARO/IL-12 by microarray analysis of 3757 genes using Atlas Glass Human 3.8 II microarray. The most highly expressed gene is cannabinoid receptor 2 (CB2), which is expressed 8 fold higher in ARO/IL-12 cells than ARO cells. CB2 agonists such as JWH-133 and JWH-015, and mixed CB1/CB2 agonist WIN-55,212-2 can induce significantly higher rate of apoptosis in ARO/IL-12 cells

than ARO cells. Similar results were obtained when ARO cells were transfected with CB2 transgene (ARO/CB2). A considerable regression of thyroid tumors generated by inoculation of ARO/CB2 cells was observed in nude mice following local administration of JWH-133 at 50 µg/day. We also demonstrated significant increase in the induction of apoptosis in ARO/IL12 and ARO/CB2 cells following incubation with 15 nM paclitaxel, indicating that tumor cells were sensitized to chemotherapy following CB2 overexpression. These data suggest that CB2 overexpression may contribute to the regression of anaplastic thyroid tumor in nude mice following IL-12 gene transfer. Given that cannabinoids have shown antitumor effects in many types of cancer models, CB2 may be a viable therapeutic target for the treatment of anaplastic thyroid carcinoma.

### Project title: Investigation Of *Braf* Mutation In Thyroid Carcinoma From Saudi Population (RAC #2050 048)

**Investigators:** Yufei Shi and Minjing Zou

#### Project description

*BRAF* is a serine/threonine kinase that serves as an immediate downstream effector of RAS in the RAS-RAF-MEK-ERK-MAP kinase-signaling cascade. Oncogenic mutations in *BRAF* are common in human cancers and nearly all of which are the T1799A transversion in exon 15 of the gene, resulting in <sup>V600E</sup> mutation (previously named V599E) in the protein. This mutation is believed to produce a constitutively active kinase by disrupting hydrophobic interactions between residues in the activation loop and residues in the ATP binding site. Activating *BRAF* mutations have recently been reported in 28% to 83% of papillary thyroid carcinomas (PTC). However this has not been studied in the Arab population. In addition functional potential of the *BRAF* pseudogene has not previously been considered. We investigated *BRAF* mutation and its pseudogene activation by direct sequencing of PCR and Real Time-PCR products of 68 thyroid tumors from Saudi Arabia: 16 multinodular goiters, 43 classic PTCs, 6 follicular variants of PTC (FVPTC), and 3 anaplastic thyroid carcinomas (ATC).

#### Progress

*BRAF*<sup>V600E</sup> mutation was detected in 20 out of 43 PTC, and all 3 ATC. No mutation was found in 16 multinodular goiters and 6 FVPTCs. There is a higher frequency of *BRAF* mutation in classic PTC patients with stage III

and IV tumors as compared to stage I and II. *BRAF* pseudogene transcripts were detected in 7 multinodular goiters, 18 classic PTC, and 1 FVPTC. There is an inverse correlation between *BRAF* pseudogene activation and *BRAF* mutation. The pseudogene transcripts were more frequently detected in tumors without *BRAF* mutation than those with *BRAF* mutation. Furthermore, overexpression of the *BRAF* pseudogene in NIH3T3 cells could activate the MAP kinase signaling pathway, transform NIH3T3 cells *in vitro*, and induce tumors in nude mice. We conclude *BRAF* mutations are specific to classic PTC and contribute towards disease progression to poorly differentiated and anaplastic thyroid carcinomas. *BRAF* pseudogene activation may also play a role in early stage tumor development.

**Project title: Clinical Evaluation And Genetic Study Of A Saudi Family With Familial Primary Cortisol Resistance (RAC #270003).**

**Investigators:** Hussein Raef, and Yufei Shi

#### Project description

Glucocorticoids are vital steroid hormones with wide spectrum of functions. These functions are largely mediated through the glucocorticoid receptor (GR). The GR binds glucocorticoid hormones in the cell cytoplasm, translocates to the nucleus, and regulates gene expression. Glucocorticoid resistance is a rare sporadic or familial condition that is characterized by generalized, partial resistance to glucocorticoids, usually without clinical evidence of hyper- or hypocortisolism. Affected individuals will have compensatory elevation in ACTH and cortisol levels that fail to suppress normally by dexamethasone. The effect of very high cortisol level on renal tubules and the increase in mineralocorticoids

due to excessive ACTH stimulation will typically result in hypertension and hypokalemic alkalosis. Excess androgens could result in precocious puberty in affected males and hirsutism and irregular menses in affected females. Irritability and weakness were also reported as symptoms in affected individuals. The clinical picture can vary from mild to severe. We aimed to understand the reasons for different phenotypes (severe to asymptomatic) observed in a family with primary cortisol resistance.

#### Progress

The genotype leading to cortisol resistance in the family members was investigated and correlated to the clinical phenotype. Genomic DNA from peripheral lymphocytes was isolated from family members. The entire GR- $\alpha$  coding sequence (exon 2-9) was amplified by PCR and sequenced. Homozygous G679S mutation was found in three clinically affected subjects. Three heterozygous sequence variations were found in the father and two siblings: G66A (E22E), G68A (R23K) and G2035A (G679S). Mother and one sibling had only heterozygous G679S mutation in one allele with no polymorphism on the other allele (wild type). The clinically unaffected subjects showed two different responses to dexamethasone. Those with heterozygous G679S mutation and ER22/23EK polymorphism had normal cortisol suppression, whereas those with heterozygous G679S mutation and wild type allele failed to suppress normally. We conclude that a homozygous G679S mutation of the GR- $\alpha$  gene is associated with severe cortisol resistance, whereas a heterozygous mutation of the same gene can lead to subclinical cortisol resistance. The effect of the heterozygous mutation was abolished in subjects carrying the ER22/23EK polymorphism.



Research Unit

**METABOLIC DISEASES  
RESEARCH UNIT /  
BIOCHEMICAL GENETICS**

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*Head*

**Osama Al-Dirbashi  
Dr. Ali Al-Odaib**

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## RESEARCH PROJECTS

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**Project title:** Analysis Of N-Acetylaspartic Acid In Amniotic Fluids And Urine For Prenatal And Postnatal Biochemical Diagnosis Of Canavan Disease By Liquid Chromatography Tandem Mass Spectrometry. RAC # 2060017 (Ongoing)

**Principal Investigator:** Osama Al-Dirbashi  
**Co-investigators:** Mohamed Rashed, Wesam Kurdi, Moeen Al-Sayed, Faiqa Intiaz,

An LC-MS/MS analytical method was developed and validated for N-acetylaspartic acid in amniotic fluids and urine. Age-matched reference ranges were generated in urine. Amniotic fluid samples from controls and from an affected sample were successfully analyzed.

**Project title:** Development Of A New Approach For The Diagnosis And Characterization Of Peroxisomal Disorders In The Saudi Population. RAC # 2070012 (Ongoing)

**Principal Investigator:** Osama Al-Dirbashi  
**Co-investigators:** Mohamed Rashed, Zuhair Al-Hassnan, Aziza Chedrawi, Tomofumi Santa

A method to analyze very long chain fatty acids, phytanic and pristanic acid in plasma as benzofurazan derivatives by LC-MS/MS was developed. The method was fully validated and was capable to detect at least nine peroxisomal disorders within a five-minute run. The method is currently used for routine analysis in our lab and we are looking into its potential to differentiate between these nine disorders based on patterns of abnormality.

**Project Title:** Newborn Screening For Hepatorenal Tyrosinemia In The Saudi Population Using A Second Tier Assay For Succinylacetone-A Two Year Study. RAC # 2070001 (Ongoing)

**Principal Investigator:** Osama Al-Dirbashi  
**Co-investigators:** Mohamed Rashed, Mohamed Al-Amoudi, Lujane Al-Ahaideb, Moeen Al-Sayed, Zuhair Al-Hassnan, Zuhair Rahbeeni, Hamad Al-Zaidan, Mohamed Al-Owain

We developed a one-minute assay using UPLC-MS/MS to determine succinylacetone in newborn screening samples that show elevated tyrosine or methionine. A manuscript (Pub # 2080027) was recently accepted for publication in Biomedical Chromatography.

**Project title:** Pre-implantation Genetic Diagnosis for the Most Prevalent Metabolic Disorders in Saudi Arabia. RAC Project # 2021023

**Investigators:** Ali Al-Odaib, PhD, Aida Al Aqeel MD, Serdar Coskun PhD, Pinar Ozand, MD PhD, Nadia Sakati MD

This project attempts to prevent the occurrence of inherited disorders by applying the Preimplantation Genetic Diagnosis (PGD) to selected genetic disorders. The following diseases are common in the Kingdom and each pose a major difficulty in its management either due to unrewarding results or due to the cost involved. Several known and novel mutation were detected in genes causing these diseases.

**Relationships Between Serum Resistin And Leptin Levels, Body Mass Index, Lipid Profile, Polymorphisms In The Resistin Gene Promoter And Leptin Receptor Gene In Obese Saudi Children** RAC # 2050030

**Investigators:** Maha Dagestani PhD, Ali Al-Odaib PhD, Namig Kaya PhD, Abdullh Al-Herbish MD, Ali Al-Zahrani MD, Rawdah Sunbul MD.

Children obesity is a complex trait influenced by interacting environmental hormonal and genetic factors. Resistin is a novel adipocyte-secreted hormone that has been proposed to be the link between obesity and diabetes, although little appears to be known regarding the physiological role of resistin in human. We are exploring the relationship between serum levels of resistin and leptin and certain anthropometric and metabolic parameters, and evaluate the associations between body composition variables and three common leptin receptor gene polymorphisms (K109R, Q223R, and K656N) and C/G SNP in promoter of RETN gene.

**Leptin Level, Leptin Receptor Gene Polymorphism And Reproductive Hormones In Saudi Females With Polycystic Syndrome** RAC # 2020030 (Completed)

**Investigators:** Maha Daghestani PhD, Ali Al-Odaib PhD, Pinar Ozand MD PhD, Ahmed Al-Himadi PhD

In this project we demonstrated the following: Insulin levels were significantly high in obese group which confirmed that obesity in Saudi women is associated with hyperinsulinemia and insulin resistance. An Association between the Q223R polymorphism of the leptin receptor gene and obesity in overweight and obese Saudi women was detected. The common pentanucleotide

polymorphism of the 3'-untranslated region of the leptin receptor gene is associated with serum insulin levels in Saudi Females with polycystic ovary syndrome. A single nucleotide polymorphism (1058 C/T) in the tyrosine kinase domain of the INSR gene was associated with one subtype of PCOS. Other susceptibility genes and environmental factors contributing to the expression of PCOS remain to be delineated. Our findings support the hypothesis that alterations in the leptin signaling system could contribute to serum insulin levels, also the obesity in Saudi Females are influenced by the leptin receptor gene 3'-UTR polymorphism.

**Knowledge And Attitude Towards The Hemoglobinopathies Premarital Screening Program In Saudi Arabia: Population Based Survey (Proposal #2061056)**

**Investigators:** Ayman Al-Suleiman

Genetic screening is an important tool to control, minimize and prevent genetic disorders in communities. Saudi Arabia had started the first national premarital screening program after the Saudi Royal Decree in 1424 to control inherited hemoglobin disorders, which consider the commonest inherited genetic disorders in the kingdom. It was the aim of this study to assess the knowledge perception and attitude among Saudi population about the premarital screening program. The study population consists of three groups. A group represent general population, a group couples presenting before premarital screening, and a group of couples who had received their results. A total of 1047 candidates were included in the study divided equally on the three study groups. There was a fair knowledge among participants of the three groups about the nature of the tests and the targeted disorders. There was a consensus about the disorders that should be included in the future PMS, >80% believe that the PMS should include both sexually and genetically transmitted diseases. The concept of genetic counseling was liked by most of the participants, however, only 34.2% of all participants had a genetic counseling before tests and only 8% had counseling after results. This study highlighted the importance of genetic counseling to improve the perception and attitude. There is agreement to expand the tests to include sexually transmitted diseases. There is a tendency to accept the obligation of prevention of the mismatched cases to proceed for marriage.

**Pre-implantation Genetic Diagnosis in Saudi Arabia: Parents Experience and Attitudes (Proposal #2041078)**

**Investigators:** Ayman Al-Suleiman

Preimplantation genetic diagnosis (PGD) has been proposed as a valuable alternative to prenatal diagnosis (PND) to select genetically 'normal' human embryos and transfer them to the uterus of a woman. Debate has occurred over the implication of PGD, safety of embryonic manipulation, effectiveness and what it would mean to live in a society where one's genetics become more a matter of choice than chance. This study evaluates a range of social and moral concerns of Saudi couples with and without experience of the *in vitro* fertilization (IVF) procedure might have about the various procedures available. A total of 184 subjects attending the King Faisal Specialist Hospital and Research Centre in Riyadh were interviewed using a semi-structured questionnaire. 87 of the subjects have complete at least one cycle of the IVF procedure. Forty-nine (100%) of the oncology group and forty-three (90%) of the ENT group were personally accept PGD technology. All the oncology and ENT group who would personally consider PGD were willing for others to be offered the procedure. Specific concerns about PGD related to the IVF procedure, waiting for the pregnancy results and egg collection were the most commonly mentioned concerns. All the groups of the subjects (100%) agreed that the destruction of an embryo prior to implantation less wrong than destruction of the fetus inside the uterus in comparison to only 30% of the PGD group. Views were more mixed for the other IVF procedure. The outcomes of this study demonstrate that PGD might be considered as a valid alternative to prenatal diagnosis. However, couples referred for PGD must be selected and counseled appropriately, considering the complexity of the treatment and the relatively low take-home baby rate.

**OTHER PROJECTS**

**Molecular Genotyping Of Hemophilia A Among Saudi Patients.**

**Investigators:** Owaidah T, Al-Odaib A, Al-Zahrani H, Al-Saleh H.

**L-2-Hydroxyglutaric Aciduria: Clinical, Biochemical And Molecular Analysis In A Large Saudi Family (RAC # 2050013).**

**Principal Investigator:** Moeen Al-Sayed  
**Co-investigators:** Eissa Faqeeh, Muhammad Faiyaz-UI-

Haque, Osama Al-Dirbashi, Hisham Dalaan, Abdelghani Tbakhi, Mohamed Al-Owain, Mohamed Rashed, Mehmet Sait Inan.

**Clinical, Biochemical And Molecular Profiles Of Saudi Patients With Dihydropyrimidine Dehydrogenase Deficiency (RAC # 2050021)**

**Principal Investigator:** Zuhair Al-Hassnan

**Co-investigators:** Muhammad Faiyaz-UI-Haque, Mohamed Al-Owain, Amal Saadallah, Osama Al-Dirbashi, Zuhair Rahbeeni, Moeen Al-Sayed, Abdelghani Tbakhi.

Research Unit

# **CARDIOVASCULAR AND PHARMACOGENETICS**

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*Head*  
**Nduna Dzimiri**

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## RESEARCH PROJECTS

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### **Project title: Evaluation Of The Relevance Of Single Nucleotide Polymorphism For Coronary Artery Disease In The Saudi Population (Project 2010020)**

**Investigators:** Nduna Dzimiri, Futwan Al-Mohanna, Maie Al-Shahid and Brian Meyer

#### **Project description**

This study focuses on identifying single nucleotide polymorphism (SNPs) and haplotypes in candidate genes for the risk of CAD using the Saudi population as a study model. The project aims at first identifying SNPs in the general population followed by the establishment of their relevance in predisposing individuals to acquiring coronary artery disease in the Saudi population.

#### **Progress**

During the report period, several novel SNPs have been identified in the a number of genes including the proteasomal  $\alpha$ -subunit type 6 (PSMA6), peroxisome proliferator-activated receptor, liver X receptor, proprotein convertase subtilisin/kexin type 9, paraoxonase, myocyte enhancer factor-2 and human endothelial transcription factor GATA2. The presence of the individual SNP was established by sequencing the coding and intron-exon junctions of the genes involving at least 100 individuals. SNPs showing associations of potential interest with the disease or displaying a prevalence of at least 5% in the general population were then considered for further studies. Currently, these SNPs are being haplotyped for association with CAD in larger populations. Thus far, we have reported an association of a common haplotype in the chromosomal region 14q13.2 encompassing the PMSA6 and KIAA0391 genes with CAD and myocardial infarction, respectively, possibly suggesting a common pathway for CAD and some of its risk factors.

### **Project # 2030012: Relevance Of Lipid Metabolizing Proteins In The Treatment Of Hypercholesterolemia And Coronary Heart Disease.**

**Investigators:** Nduna Dzimiri, Futwan Al-Mohanna, Maie Shahid and Brian Meyer

#### **Project description:**

This study aims at identifying mutations in candidate genes for intra-individual differences in patient responses

to drug therapy of antihypercholesterolemia treatment with statins (lipid lowering agents) and hypertension therapy with losartan in a target population of about 3,000 patients. Selected candidate genes for the statin study include 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), cholesteryl ester transfer protein (CETP), 3-hydroxy-3-methylglutaryl-coenzyme A reductase Liver X cytochrome P450 subtype CYP3A4, receptor alpha subtype gene (LXR $\alpha$ ), sterol regulatory element-binding protein subtype 2 (SREBP-2) and the SREBP cleavage-activating protein (SCAP).

#### **Progress**

During the last period we studied the relationship of the SREBP-2 Ala595Gly and SCAP Ile796Val with response to simvastatin therapy. While our data thus far do not appear to indicate any significant association of these two SNPs with the intraindividual differences in patient response to therapy, they suggest that these two polymorphisms play functionally discrete roles, both independently and possibly interactively, in causing lipid metabolic disorders. We should be able to obtain more informative results in larger population sizes. We also examined the role of two SNPs rs2740574 and rs12721620 in patient responses to simvastatin therapy. Our preliminary data point to strong associations of both the rs2740574 ( $p < 0.001$ ) and the rs12721620 ( $p < 0.001$ ) with a reduction in cholesterol and low density lipoprotein, and of the heterozygote C/T ( $p < 0.04$ ) of the rs12721620 with reduction in triglycerides and cholesterol, following treatment with simvastatin.

### **Project # 2050035: Clinical And Molecular Characterization Of Patients With Inherited Arrhythmogenic Disorders**

**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 a number of clinical objectives including confirmation of patient diagnosis stratification and prophylactical strategies in the management of patients with arrhythmogenic disorders.

**Progress**

Two families have been recruited thus far for the LQTS study, and preliminary linkage analysis has been performed, possibly pointing to a novel locus on chromosome 5q31-34 as being associated with the syndrome. Further analysis to narrow down the region and identify some potential candidate genes is currently in progress. We are also trying to recruit more families to enable us narrow down the interval and to identify more novel loci for this rare autosomal recessive disorder.



Research Unit

# FIRST ARABIAN HEREDITARY DEAFNESS

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*Head*  
Faiqa Imtiaz

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## RESEARCH PROJECTS

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**Project title: Role of the DFNB1 Locus in Hereditary Deafness in the Saudi Population (RAC #2040 039 and PSCDR).**

This project aims to identify and characterize the mutations causing non-syndromic hereditary deafness in the Saudi population. To date, results indicate that mutations in the Autosomal Recessive Deafness Locus 1 (DFNB1-responsible for 50% of non-syndromic hereditary deafness worldwide) are not a significant cause of hereditary deafness in Saudi Arabia (~5%). This result has accelerated efforts to conduct prioritized linkage analysis using 10K Affymetrix SNP Chip technology in 13 families so far in which DFNB1 has been excluded. Currently out of 13 families, the disease-causing mutations have been identified in 2 families, candidate genes have been selected and are being screened for 8 families and linkage will be repeated using higher density SNP Chip technology on the remaining 3 families as linkage analysis was not conclusive.

**Project title: Molecular Analysis of Five Inherited Metabolic Disorders. Estimation of Volterra Kernels of Physiological Systems Using Meixner Function (RAC #2020 018)**

This is a combined project studying the genetic basis of five inherited metabolic disorders: Argininosuccinic Aciduria (ASA), Methylmalonic Acidemia (MMA), HMG Co-A Lyase, Propionic Acidemia (PPA) and Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD) in the Saudi population. Experimental work has concluded for ASA, HMG Co-A Lyase and VLCAD as 90-95% of disease-causing mutations have been reported. Mutations have also been found in patients with PPA (50%) and five disease-causing mutations (4 novel and 1 known) have been found in families with MMA. As the scientific aims

of this project have been achieved, the investigators have mutually agreed to close this project.

**Project title: Association of a Novel LCT Promoter SNP with Reduced Lactasephlorizin Hydrolase (LPH) Activity. (RAC # 2060 005)**

This is a collaborative project with investigators from the University of Helsinki, Finland, to determine the functional significance of a novel Single Nucleotide Polymorphism (SNP) associated with this lactase persistence in the Saudi Population. Our results have determined that the novel SNP is the only founder variant of lactase non-persistence/persistence in the Urban Saudi Arabian population and that the SNP genotypes perfectly correlate with disaccharidase activities and lactase/sucrase ratio in 25 intestinal biopsy specimens confirming its role as the founder lactase persistence allele in this population.

**Project title: Hereditary Tyrosinemia Type I: Clinical, Biochemical & Molecular Characterization. (RAC # 2050 022).**

This project aims to identify the underlying disease-causing mutations in patients with Tyrosinemia Type I in the Saudi population. To date, 9 mutations (6 novel and 3 known-accounting for ~85% coverage) have been found in patients with this disease.

**Project title: Clinical and Molecular Profiles of Saudi Patients with Medium Chain Acyl CoA Dehydrogenase (MCAD) Deficiency. (RAC # 2050 037).**

This project aims to screen for mutations causing MCAD in the Saudi population. I have identified two novel mutations that account for 93% of pathogenic mutations in Saudi MCAD patients. As the scientific aims of this project have been achieved it has now been closed and referred to the diagnostic laboratory which will undertake clinical testing as required.

Research Unit

# HEREDITARY IMMUNOLOGY

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*Head*  
**Osama Alsmadi**

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## RESEARCH PROJECTS

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### **RAC#2060012: Underlying Molecular Genetic Defects of Severe Combined Immunodeficiencies (SCID) in Saudi Arabia.**

Severe combined Immunodeficiencies (SCID) represent the most severe form of primary Immunodeficiencies. At least ten different forms of human SCID have now been recognized and can be grouped according to inheritance, phenotype, and for some of them, identification of the mutated genes. The specific aim of this study is to identify the underlying molecular genetic defects of SCID in Saudi Arabia. Based on SCID phenotype, individuals are screened for mutations in the most likely genes (11 candidate genes) that fit the clinical and laboratory presentation of SCID. Families of patient's negative for mutations of the known SCID genes who demonstrate a strong family history will be utilized for subsequent linkage analysis. Up to date, more than 42 families with SCID disease have been studied. Mutations, some novel, in RAG1, RAG2, Artemis, Jak3 and ADA genes have been identified. A few families had no identified mutations in known disease causing genes and will be candidates for whole genome linkage analysis.

### **RAC# 2040 029: Underlying Molecular Genetic Defects Of Familial Chronic Idiopathic Myelofibrosis.**

One family comprising two parents, 5 normal, and 4 affected siblings was identified with this apparently novel disorder. An Affymetrix 10K DNA chip microarray was used for whole genome linkage analysis. A LOD score of 3.1 resulted from this analysis. The linked locus is

nearly 10cM in size and encompasses the gene rich HLA locus.

### **RAC# 2030 008: Molecular Characterization Of Syndromic Hearing Loss In The Kingdom Of Saudi Arabia.**

A total of 51 samples collected from 2 families were obtained with full consent. 10K microarray DNA chip analysis was conducted on all the families. The combined analysis revealed a linkage interval of 4.6 cM with a LOD score of 5.3 on chromosome 11, between markers rs1404501 and D11S987. A strong candidate gene (FGF3) was identified in one family and contained a novel nonsense mutation. This represented only the second family identified worldwide with this novel syndromic phenotype. Additional mutation detection is underway for the second family in other members of the FGF family that are also present within the linked interval.

### **RAC # 2040 029: "Adaptation Of WGA Technology To Dry Blood Spots, An Application To Facilitate Molecular Diagnostics And Genetic Testing"**

A detailed protocol was established to generate assay-ready DNA from dry blood spots that are obtained from the metabolic diseases diagnostic laboratory. We found that 30°C & 40°C incubation conditions both support successful WGA. 23 sets of new primers were investigated under different thermal and buffer conditions for WGA reactions. A few primers were equivalent or better than the currently used primers in terms of genome coverage and overall amplification yield. Extensive studies have been completed on the efficiency of the WGA process with these novel primers and the suitability of product for genotyping using microsatellite and chip based assays.

Research Unit

# BEHAVIORAL GENETICS

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*Head*  
**Nada Al-Tassan**

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## RESEARCH PROJECTS

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**Project title: Molecular Analysis of APTX and SETX genes in Saudi Families with Ataxia Ocular Apraxia (AOA) (2050036).**

**Investigators:** Al-Tassan N, Bohlega S, Imtiaz F, Yamani S.

### Project description

The objective of this study is to identify families with the rare recessive neurological disorder AOA type I or type II, and screen for mutations in their common known genes APTX and SETX.

### Progress

Five families with AOA were identified. AOA type I (family B,C,D) and AOA type II (family A and E) with 2 or more affected individuals. Direct sequencing of the whole open reading frame (ORF) of both APTX and SETX was performed and completed in four families and is undergoing in the fifth family. 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. Families (B,C,D) have been negative for mutations in both genes indicating the possible involvement of other genes. Linkage analysis in family D (3 affected individuals) was

performed using (10K micro-array chip). A candidate region (LOD score of 3.2) harboring MRE11 gene which is implicated in AT-Like disorder was identified. Sequence analysis of MRE11 revealed a common reported mutation W210C in exon 7 in all 3 affected members of family D and the 2 affected individuals from family B. Family E (AOA2, four affected) is still under screening for mutation in reported genes.

**Project title: Genetic Mutations in Weill Marchesani Syndrome (WMS) in Saudi Arabia (2070008).**

**Investigators:** Al-Tassan N, Morales J, Bakheet D, AL-Mahrouqi R.

### Project description

The aim of this study is to identify families with WMS which is a rare connective tissue disorder, and screen for mutations in the known genes ADAMTS-10 (recessive) and FBN-1 (dominant).

### Progress

Sequencing of the whole coding region of ADAMTS-10 is being performed in affected individuals and parents in three families with recessive WMS phenotype. Mutation screening is undergoing in these families and new families identified.

Research Unit

# COGNITIVE GENETICS

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*Head*  
**Namik Kaya**

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## RESEARCH PROJECTS

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**Project title: Positional Cloning of Genes Underlying Genetic Disorders with Prominent Neurodevelopmental Manifestations in Several Extended Families. RAC # 2060 035**

**Investigators:** Namik Kaya, Moeen Al-Sayed

### Project description

The specific aim of this project is to determine gene/s or regions that are critical and likely to play role on the manifestations of genetic disorders with prominent neurodevelopmental features. We will be utilizing high density 500K Affymetrix SNP genechips to perform genotyping, copy number analysis and mapping studies on the patients.

### Progress

DNA samples were collected from six consanguineous families (affected, unaffected, and parents). Genome-wide scans performed on two families using Affymetrix 10K and 500K Mapping Assays and regions linked to the disease were identified. Currently candidate genes have been sequenced to find putative mutations and fine mapping has been performed to narrow the region linked to the disease.

**Project title: Molecular Genetic Studies in Chromosome Disorders. (RAC # 2040 042)**

**Investigators:** Namik Kaya, Pinar Ozand, Nadia Sakati, Mehmet Inan, Dilek Colak, Fowzan Alkuraya, Ali Al-Odaib, Naji Al-Dosari, Claudia Walter.

### Project description

The specific aim of this project is to identify chromosomal abnormalities of patients clinically suspected to have a chromosome disorder.

### Progress

Recently Agilent microarray system and Affymetrix's GeneChip technology were tested on the patients to see the performance of these microarrays to detect chromosomal abnormalities that cannot be detected standard high-resolution karyotyping techniques. Around 50 patients who have screened with standard karyotyping

techniques and found to have normal karyotype were screened using either microarray platform. Known and unknown novel copy number variants (CNVs) as well as telomeric deletions, complex arrangements in the patients were identified. A database is being created as it was proposed in the project. A few manuscripts comprising our findings are in preparation. The database will include all the CNVs and their frequencies found in the Saudi population.

**Project title: Molecular Characterization of Autism Spectrum Diseases: A Pilot Study for Three Distinct Disorders. (RAC # 2040-024)**

**Investigators:** Namik Kaya, Mehmet Sait Inan, Pinar Ozand, Nadia Sakati, Dilek Colak, Ali Al-Odaib, Omer Demirkaya

### 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 we have selected several disorders within the autism spectrum diseases phenotypically different but all of which manifest autism. These are Fragile-X with autism, rett syndrome, osteopetrosis with autism, and very early and severe infantile autism. The aforementioned hypothesis will try to determine common gene/s among these four types of the diseases

### Progress

Genome-wide 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 were performed. Differentially and significantly expressed few genes that are common among the autism spectrum diseases were determined. One of these genes is involved in chromosome inactivation and imprinting and severely down-regulated among all the autistic patients (regardless of having fragile-X or rett or osteopetrosis). Currently confirmation studies using realtime RT-PCR are performed.

**Project title: Pathogenesis of Early Infantile Primary Lactic Acidosis (RAC # 2050-009)**

**Investigators:** Mohammad Al-Owain, Namik Kaya, Pinar Ozand, Khaled Abu-Amero, Ali Al-Odaib, Mehmet S. Inan, Abdulghani Tbakhi, Dilek Colak, Zuhair Al-Hasnan

**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. For the microarray analysis ABI 1700 Microarray Analyzer is used to determine the gene signatures in whole blood and identify key genes unknown to participate in the nuclear / mitochondrial dialogue for this disease.

**Progress**

Genome-wide gene expression studies were performed on patients' RNA isolated from whole blood. Mitochondrial activity as well as apoptosis status of lymphoblastoid cell lines were determined. mtDNA was completely sequenced to identify putative mutations. The results from expression studies identified critical genes that are significantly dysregulated in patients vs controls. A few mutations were also found in mtDNA. Our findings indicated the presence of mitochondrial dysfunction but this needs to be confirmed with more accurate assays. Currently, realtime RT-PCR studies are performed to confirm microarray results.



# **HUMAN CANCER GENOMIC RESEARCH**



The Department of

# HUMAN CANCER GENOMIC RESEARCH

The mission of the Department of Human Cancer Genomic Research 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 Affymetrix, tissue micro array & high throughput sequencing analyzer. The main mission of this department is also to design better strategies to diagnose, prognosticate & treat neoplasm that are specifically relevant to Saudi Arabia as compared to the Western population.

The year 2007 has been very productive scientifically during which we were able to integrate three major components of our laboratory studies to come up with answers relating to neoplasm that are more prevalent in the Kingdom of Saudi Arabia. Clinical research using tissue microarray as well as patient's clinical history combined with *in-vitro* studies using cell lines to study the functional aspects of these cancers and finally correlating these findings *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 will definitely enhance and improve the chances of treating these cancers using targeted therapy against certain genes that are being discovered with the help of these techniques.

## **Director**

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

## **Scientific Staff:**

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Saad Al Odaib  
 Maria Victoria Concepcion  
 Selah Fulgencio  
 Myra Maningas

Using the above-mentioned strategy, we were able to detect multiple genetic targets in colo-rectal carcinoma, thyroid cancers, diffuse large B-cell lymphomas and ovarian cancers that can be utilized in improving the overall survival in patients suffering from these cancers.

The Department of Human Cancer Genomic Research is further divided into 3 closely inter-related sections.

1. Section of Experimental Pathology
2. Section of Molecular Oncology
3. Biological Repository Center

### Section of Experimental Pathology

During the year 2007 the section of Experimental Pathology has been able to identify different genetic targets can be utilized as either diagnostic markers or as therapeutic targets. These include the detection of cyclin H as an independent prognostic marker in Diffuse Large B-Cell Lymphoma, identification of a sub-group of papillary thyroid cancer that have over-expression of Fatty acid synthase (FAS), that can be used as targeted therapy for these cancers. We are utilizing the latest technology to study these cancers. We are actively collaborating nationally and internationally with other scientific groups to achieve our objectives.

### Section of 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.

In close collaboration with the section of experimental pathology, we are studying the functional aspects of different cancers with respect to their survival and apoptotic pathways. We are utilizing the data that is being generated by the department of experimental pathology to study in detail, the functional aspects of different genes that are being identified. Using a more specific approach by either using specific inhibitors against these genes or silencing of these genes by siRNA, we are activating different apoptotic pathways that can be used to

induce cell death in these tumors. We further confirm these data *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 tumour 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

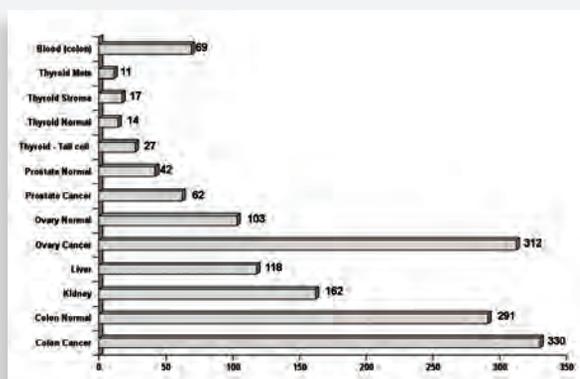
Collect and maintain archives of frozen tissues (normal and neoplastic), serum, paraffin blocks and commercial cell lines.

### Activities

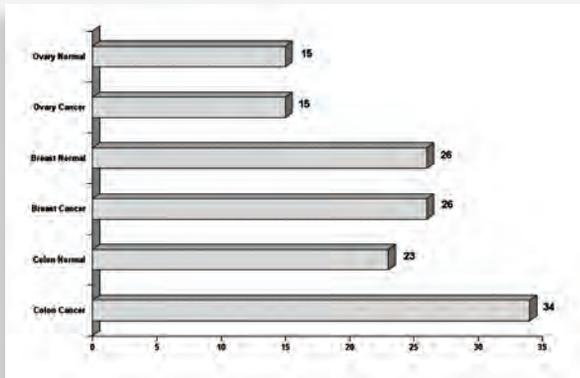
BRC is handling a number of different projects in which biological samples are being optimally stored and further processing is being done as and when requested by the researchers.

1. Processing biomaterial (DNA and/or RNA extraction from blood, frozen tissues and paraffin blocks) for various research projects – a total

DNA Extraction from TMA samples



RNA extraction from fresh / frozen samples



of 1697 specimens were processed in the year 2007.

2. Cell blocks prepared from cell lines used for immunohistochemistry -18
3. Cell lines prepared for protein extraction - 56
4. Commercial cell lines expanded and grown in bulk over 1500 vials frozen and stored in liquid nitrogen.
5. 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.

Number of samples processed

Paraffin blocks	4000
H & E stain	4000
Immunohistochemistry	2000
Frozen section	500

6. Storing biomaterial under controlled temperature:

- Storage of various commercial cell lines which are

being used for various ongoing research projects in our department

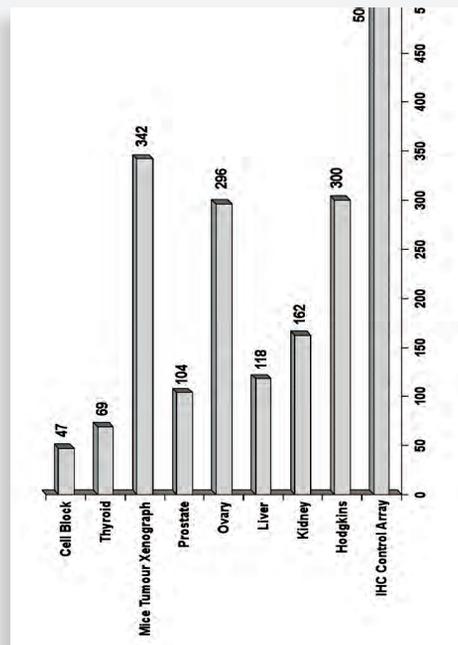
- Maintaining supply of liquid nitrogen for cryomed freezers for Department of Genetics, Research Centre
- Storage of tissues for project # 2060-007.

7. Maintaining and distributing commercially available cell lines (ATCC) to the research investigator/clinicians with RAC approved projects.

### Tissue Microarray (TMA) Unit

Department of Human Cancer Genomics Research has firmly established TMA technology and has an extensive archival of tumour specimens in a TMA format. A total of 1938 tumour and normal tissue specimens were arrayed in a

TMA format in year 2007. In addition we have a cell line block TMA.



## RESEARCH PROJECTS

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There are five active RAC approved projects for the year 2007.

1. Role of PI3-kinase-AKT pathway in epithelial carcinomas. (RAC 2070 004)
2. Molecular signatures of Diffuse large B-cell lymphoma (DLBCL), Lung and Ovarian Cancer; A pilot study. (RAC 2060 008)
3. Molecular signatures of Cancer; Clinical significance in Saudi Arabian and European cancer patients. (RAC 2040 004)
4. Role of JAK/STAT and PI3-kinase pathways in Hematological malignancies. (2040 014)
5. Translational initiatives in Hematological malignancies. (2020 015)

The DHCGR is actively involved in programs relating to four different organ sites:

1. Hematological Malignancies
2. Thyroid
3. Colon
4. Ovary

## HEMATOLOGICAL MALIGNANCIES

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**Investigators:** Khawla S. Al-Kuraya, Shahab Uddin, Prashant P. Bavi, Maqbool Ahmed, Abdul K. Siraj, Jehad Abubaker, Azhar R. Hussain, Zeenath Jehan.

### i. Lack of cyclin H expression is Independent Prognostic Marker for Poor Outcome in Diffuse Large B-Cell Lymphoma

#### Project description

Diffuse large-B-cell lymphoma (DLBCL) is the most common lymphoid malignancy in adults, accounting nearly 40% of all non-Hodgkin's lymphomas. Since combination chemotherapy cures only 40-50% of the patients, the identification of prognostic markers could help to develop risk-adapted treatment strategies. As proliferation of cells is essential for tumour growth, analysis of the cell cycle and its individual phases might give additional information on tumour progression and

clinical behavior. Cyclin H is a substrate of protein kinase 2, a ubiquitously expressed serine/ threonine kinase required for cell viability and cell cycle progression. Cyclin H occurs as a component of the cyclin H/Cdk 7/Mat 1 complex. Cdk 7 regulates cyclin H and this complex phosphorylates Cdk 1, 2, 4 and 6 leading to upregulation of kinase activity. Cyclin A, B, D3 and E have been studied in DLBCL and have shown to have a prognostic value. We evaluated for the first time the expression of cyclin H (1:300, Catalogue # 2927, Cell Signaling Technology, USA) by immunohistochemistry in 301 diffuse large B-cell lymphomas in a tissue micro array format. We also studied expression of the cell cycle regulatory molecules p27 (1:100, clone IB4, Dako, Glostrup, Denmark) & p21 (1:200, clone SX-118, Dako, Glostrup, Denmark ) by immunohistochemistry. Cyclin H expression was seen in 85.7 % of the DLBCL and was correlated with p27 expression ( $p < 0.0001$ ) & p21 expression ( $p = 0.0253$ ). Our results show that nuclear expression of cyclin H expression in >30 % of tumor cells were significantly associated with better overall survival, both in the univariate ( $p = 0.0008$ ) and multivariate analysis ( $p = 0.0220$ ). Furthermore its prognostic significance was independent of International Prognostic Index ( $< 0.0001$ ). Cyclin H expression by IHC is easy to evaluate on paraffin sections and the high prognostic value of cyclin H may be basis for future prospective trials. In addition, high prevalence of cyclin H expression suggests a possible target for individualized therapy.

#### Progress

Manuscript in press. Human Pathology 2007.

### Genetic Polymorphisms of Methylene tetrahydrofolate Reductase and Promoter Methylation of MGMT and FHIT Genes in Diffuse Large B-Cell Lymphoma Risk in the Middle East.

Diffuse large B-cell lymphoma (DLBCL) is one of the most common non-Hodgkin's lymphoma types. Methylene tetrahydrofolate reductase (MTHFR) balances the pool of folate coenzymes in one carbon metabolism of deoxyribonucleic acid (DNA) synthesis and methylation; both are implicated in carcinogenesis of many types of cancer including lymphoma. Two common variants in the MTHFR gene (C677T and A1298C) have been associated with reduced enzyme activity, thereby making MTHFR polymorphisms a potential candidate as a cancer-predisposing factor. The O(6) methylguanine DNA

methyltransferase (MGMT) and fragile histidine triad (FHIT) genes are transcriptionally silenced by promoter hypermethylation in DLBCL. These genetic differences are highly race specific and have never been screened in the Saudi DLBCL patients. We conducted a hospital-based case-control study including 160 DLBCL cases and 511 Saudi control samples analyzing the MTHFR C677T and A1298C functional polymorphisms by the restriction fragment length polymorphism method and their association with MGMT and FHIT genes promoter hypermethylation. Our data demonstrated that Saudi individuals carrying MTHFR genotype 1298CC ( $p < 0.001$ ) and the 1298C allele ( $p = 0.012$ ) had 4.23 and 1.73-fold higher risk of developing DLBCL, respectively. Additionally, combined genotype CCCC (MTHFR 677CC + MTHFR 1298CC) was associated with 3.489-fold, and CTCC (MTHFR 677 CT + 1298CC) was related to 9.515-fold higher risk, compared with full MTHFR enzyme activity. No significant association between MTHFR variant genotypes and methylation of MGMT and FHIT genes were observed. Our findings suggested that polymorphisms of MTHFR enzyme genes might be associated with the individual susceptibility to develop DLBCL. Additionally, the results indicated that MTHFR variants were not related to MGMT or FHIT hypermethylation in DLBCL.

#### Progress

Manuscript published in *Ann Hematol.* 2007 Dec; 86 (12): 887-895

#### Sanguinarine-Dependent Induction of Apoptosis in Primary Effusion Lymphoma Cells

##### Project description

Primary Effusion Lymphoma (PEL) is an incurable, aggressive B-cell malignancy that develops rapid resistance to conventional chemotherapy. In efforts to identify novel approaches to block proliferation of PEL cells, we found that sanguinarine, a natural compound isolated from the root plant *Sanguinaria canadensis*, inhibits cell proliferation and induces apoptosis in a dose dependent manner in several PEL cell lines. Our data demonstrate that sanguinarine-treatment of PEL cells results in up-regulation of death receptor5 (DR5) expression via generation of reactive oxygen species (ROS) and causes activation of caspase-8 and truncation of Bid. Subsequently, tBid translocates to the mitochondria causing conformational changes in Bax, leading to loss of mitochondrial membrane potential and

release of cytochrome c to the cytosol. Sanguinarine induced release of cytochrome c results in activation of caspase-9, -3, and polyadenosin-5'-diphosphate-ribose polymerase (PARP) cleavage leading to induction of caspase-dependent apoptosis. In addition, we demonstrate that pre-treatment of PEL cells with z-VAD-fmk, a universal inhibitor of caspases abrogates caspase and PARP activation and prevents cell death induced by sanguinarine. Moreover, treatment of PEL cells with sanguinarine down-regulates expression of inhibitor of apoptosis proteins (IAPs). Finally, NAC, an inhibitor of ROS, inhibits sanguinarine-induced generation of ROS, up-regulation of DR5, Bax conformational changes, activation of caspase-3 and down-regulation of IAPs. Taken together, our findings suggest that sanguinarine is a potent inducer of apoptosis of PEL cells via up-regulation of DR5 and raise the possibility that this agent may be of value in the development of novel therapeutic approaches for the treatment of PEL.

#### Progress

Manuscript published in *Cancer Research* 2007, Apr 15;67(8):3888-97.

#### Significance Of Ubiquitin Ligase Subunit Skp-2 Proto-Oncogene And Proliferative Marker Ki67 Expression In Diffuse Large B-Cell Lymphoma

S-phase kinase-associated protein 2 (SKP-2) is a proto-oncogene that has been shown to be expressed in a number of tumors. A number of studies have shown that SKP-2 plays a role in the degradation of tumor suppressor genes by increased proteasome-dependent degradation. SKP-2 overexpression is highly representative of intrinsic biological aggressiveness of certain cancers including breast, non-small cell lung cancer and gastric carcinoma, however its role in hematological malignancies have not yet been explored. Therefore, in this study we examined 100 clinical samples of diffuse large B-cell lymphoma (DLBCL) to study the expression pattern of ubiquitin ligase subunit SKP-2 proto-oncogenes and its relation to proliferative index marker protein Ki67 to correlate tumor aggressiveness. The expression of SKP-2 and Ki67 were examined by immunohistochemistry using specific antibodies on formalin-embedded tissue sections of DLBCL patients. Our data showed that SKP-2 was over expressed in majority of DLBCL and was associated with expression pattern of the proliferating index marker Ki67 protein. Since increased proteasome-dependent degradation of tumor suppressor genes play a critical

role in the etiology of various tumors and proteasome inhibition is a novel approach for treating malignancies and has been approved for clinical use, we sought to determine whether inhibition of proteasome by MG132, a specific proteasome inhibitor induces apoptosis in a panel of DLBCL cell lines. Our data showed that treatment of DLBCL cell lines by MG132 induced apoptosis in a dose dependent manner. Inhibition of proteasome also decreased the expression of SKP-2 leading to subsequent disruption of mitochondrial membrane potential causing release of cytochrome c into the cytosol. Release of cytochrome c resulted in activation of caspase-3 and cleavage of PARP ultimately leading to apoptosis. These data suggests that SKP-2 expression plays a major role in the oncogenesis of DLBCL and overexpression of SKP-2 can be used as useful prognostic marker. Furthermore, proteasome inhibitors can be used as future therapeutic modality in treating DLBCL.

#### Progress

Abstract accepted as a poster for 49th ASH 2007. December 8-11, 2007, Georgia World Congress Center, Atlanta, Georgia, USA.

#### Polymorphisms Of Drug – Metabolizing Enzymes Cyp1a1, Gstt And Gstp Contribute To The Development Of Diffuse Large B-Cell Lymphoma Risk In The Saudi Arabian Population.

The last four decades have seen significant increase in the incidence of Non- Hodgkin's Lymphoma (NHL) as a possible result of increasing environmental carcinogens exposure. Based on the increasing evidence for the association between carcinogens exposure related cancer risk and xenobiotic gene polymorphisms. We have undertaken a hospital based case control study on xenobiotic gene polymorphisms in Saudi individuals with a diagnosis of diffuse large B-cell lymphoma (DLBCL). Polymorphisms in five genes (CYP1A1, GSTT1, GSTP1, GSTM1 and NQO1) were characterized in 182 individuals with DLBCL and 513 normal controls using PCR-RFLP method. The CYP1A1\*2C ( $p=0.011$ , odds ratio 6.62 and 95% CI [1.56-28.10]), GSTT1 null ( $p<0.001$ , odds ratio 11.94, 95% CI [7.88-18.12]) and GSTP1 TT genotypes ( $p=0.017$ , odds ratio 3.42 95% CI [1.26-9.38]) demonstrated significant association of DLBCL risk. None of the other alleles tested for, proved to be significant indicators of DLBCL risk. Our findings suggest that polymorphisms of xenobiotic metabolizing enzyme genes may modify the individual susceptibility to develop DLBCL in Saudi Arabia.

#### Progress

Manuscript accepted in Leukemia and Lymphoma 2007 – in press.

#### THYROID

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**Investigators:** Khawla S. Al-Kuraya, Shahab Uddin, Abdul K. Siraj, Azhar R Hussain, Maqbool Ahmed, Prashant P. Bavi, Jehad Abubaker, Zeenath Jehan.

#### Clinicopathological Analysis Of Papillary Thyroid Cancer With Pik3ca Alterations In A Middle Eastern Population.

**Context:** Genetic aberration in PI3K/AKT pathway have been detected in numerous and diverse human cancers. PIK3CA, which encodes for the catalytic subunit of p110 $\alpha$  of PI3-kinase, is amplified in some cases of papillary thyroid cancer (PTC). Mutations in the PIK3CA have also been identified in thyroid cancers and though relatively common in anaplastic thyroid carcinoma (ATC), are uncommon in PTC.

**Objective:** To investigate genetic alterations like PIK3CA gene mutation, PIK3CA amplification, RAS and RAF mutations. To further explore the relationship of these genetic alterations with various clinicopathological characteristics in Middle Eastern PTC.

**Design:** We used FISH technique for analysis of PIK3CA amplification from 536 PTC cases and selected amplified samples were further validated by real-time quantitative PCR. Mutation analysis was done by direct DNA sequencing of PIK3CA, N2-RAS, BRAF genes.

**Results:** FISH analysis revealed the presence of PIK3CA amplification in 265 of 499 (53.1%) PTC cases analyzed; PIK3CA gene mutations in 4/207 PTC (1.9%); N2-RAS mutations in 16/265 PTC (6%); BRAF mutations in 153/296 PTC (51.7%). N-RAS mutations were associated with an early stage ( $P = 0.0465$ ) and lower incidence of extrathyroidal extension ( $P = 0.027$ ), while BRAF mutations were associated with metastasis ( $P = 0.0274$ ) and poor disease free survival ( $P = 0.0121$ ) in PTCs.

**Conclusion:** A higher incidence of PIK3CA alterations and the possible synergistic effect of PIK3CA alterations and BRAF mutations suggest their major role in Middle Eastern PTC tumorigenesis and argue for therapeutic

targeting of PI3K/AKT and MAP kinase pathways.

### Progress

Manuscript accepted in *J Clin Endocrinol Metab.* 2007 Nov 13; [Epub ahead of print]

#### **Genome-Wide Expression Analysis Of Middle Eastern Papillary Thyroid Cancer Reveals c-MET As A Novel Target For Cancer Therapy.**

### Project description

**Objectives.** To screen and validate the global gene expression in the Middle Eastern papillary thyroid carcinoma (PTC) using cDNA expression arrays and immunohistochemistry (IHC) on tumor tissue microarrays (TMA) in an attempt to find genes may be of importance in malignant progression of PTC in the Middle East which therefore can be targeted in cancer therapy.

**Experimental Design:** Twenty-nine (29) PTC tissue specimens were compared with 7 morphologically normal thyroid specimens by use of HUG133-Plus2.0 gene cDNA microarray. Results for selected genes were confirmed by reverse transcription-PCR (RT-PCR). Protein expression of selected genes was further studied using tissue microarray consisting of 500 PTC and compared with histological normal thyroid tissue samples.

**Results:** There were 194 genes over-expressed in PTC tissue relative to normal thyroid tissue. The genes that were up regulated in PTC were involved in cell cycle regulation, cell signaling and oncogenesis. Among these genes, c-MET was identified by immunohistochemical methods as protein that is over expressed in 40% of PTC and was significantly associated with more aggressive behavior e.g. higher stage, extensive nodal involvement and tall cell variant.

**Conclusion:** Our data suggests that c-MET dysregulation is associated with aggressive behavior and may serve as molecular biomarker and potential therapeutic target in this disease.

### Progress

Manuscript accepted in *J Pathol.* 2007 Oct;213(2):190-9.

#### **ii: Fatty Acid Synthase Is A Potential Target For A Sub-Group Of Papillary Thyroid Cancer Therapy.**

Fatty acid synthase (FAS) is an enzyme that plays critical role in de novo synthesis of fatty acids. FAS is overexpressed in a number of human cancers but its role has not been elucidated in papillary thyroid carcinoma (PTC). We therefore investigated the role of FAS in PTC using a panel of cell lines, clinical samples and nude mouse model. Using tissue microarray technology immunohistochemistry was done on 536 samples, and our data shows that expression of FAS is associated with activated AKT (p-AKT). Our in vitro study show that treatment of PTC cell lines (NPA-187, ONCO-DG-1, B-CPAP1) with C-75, an inhibitor of FAS suppresses growth and induces apoptosis in all cell lines. Treatment of PTC cells with C-75 causes downregulation of FAS and inactivation of AKT activity leading to apoptosis. Further downstream, C-75 induces activation of caspase-8 and cleavage of Bid subsequently leading to loss of mitochondrial membrane potential and release of cytochrome c from mitochondria into cytosol, resulting in activation of caspase-3 and cleavage of PARP. zVAD-fmk, a universal inhibitor of caspases prevents caspase-3 activation and abrogates apoptosis induced by C-75. In addition, treatment of PTC cells with C-75 downregulates the expression of antiapoptotic proteins, XIAP, cIAP1 and survivin. Finally, treatment of NPA-187 xenografts with the C-75 resulted in growth inhibition of tumors in nude mice via downregulation of FAS expression. Altogether, these results suggest that FAS and activated AKT pathway may be a potential target for therapeutic intervention for the treatment of PTC.

### Progress

Manuscript submitted to *Annals of Surgery* 2007.

## COLON

**Investigators:** Khawla S. Al-Kuraya, Shahab Uddin, Jihad Abubaker, Prashant P. Bavi, Zeenath Jehan, Azhar R. Hussain, Maqbool Ahmed.

#### **i: Correlation Of Pi3kca Mutation And Microsattelite Instability In Colorectal Carcinoma From Middle East.**

Activation of the phosphatidylinositol 3'-kinase (PI3K)/AKT pathway results in an increase in cell proliferation, survival. Somatic mutations within the PI3K catalytic subunit, PIK3CA are common cause of increasing PI3K activity and are believed to be oncogenic in many cancer types. Few reports addressed the association between PIK3CA mutations and tumor progression specifically in

Microsatellite instable (MSI) colorectal cancer (CRC). In the present study, we have evaluated PIK3CA mutational status in a series of 410 Middle Eastern CRC and 13 colon cell lines to study the prevalence of PIK3CA mutations in MSI cases, PTEN expression in CRC, and possibility of therapeutic targeting of this set of patients. PIK3CA mutations were found in 4 of the cell lines tested and 51 colorectal carcinomas (12.2 %). Three of these 4 mutated cell lines were MSI. PTEN was inactivated in 66.1% of the CRC. Furthermore, we observed a strong association between PIK3CA mutations and MSI status ( $P = 0.0046$ ) while PTEN loss was more frequent in microsatellite stable (MSS) CRC ( $P = 0.043$ ). A high prevalence of genetic alterations in PI3K/AKT pathway in Saudi cohort of CRC, predominance of PIK3CA mutations in the MSI subgroup and their possible involvement in development/progression of this subset of CRC are some of the significant findings of our study.

#### Progress

Manuscript accepted in *Oncogene* 2007. In press.

#### Genomic Instability Pathways In Colorectal Carcinomas Of Saudi Arabia, Molecular And Tissue Microarray Analysis.

**Objectives:** In the light of recent reports on genetic differences from different ethnical groups and high consanguinity rates in Saudi Arabia, we analyzed colorectal cancers (CRC) for genomic instability. The goal of this study was to evaluate the overall incidence of MSI-H, HNPCC and TP53 mutations in Saudi colorectal carcinomas.

**Methods:** We studied microsatellite instability (MSI) pathway in Saudi colorectal carcinomas (CRC) from 179 unselected patients by two methods: microsatellite analysis by PCR and immunohistochemistry (IHC) detection of MLH1 and MSH2 proteins. TP53 mutations were studied by sequencing exons 5, 6, 7 and 8.

**Results:** Of the 150 colorectal carcinomas analyzed for microsatellite instability, 16 % of the tumors showed high level instability (MSI-H), 19.3 % had low level instability (MSI-L) and the remaining 64.0 % tumors were stable. Survival of the MSI-H group was better as compared to the MSI-L or MSS group ( $p=0.0217$ ). In the MSI-H group, 48 % were familial MSI tumors which could be attributable to the high incidence of consanguinity in the Saudi population. TP53 mutations were found in 23.9 % of the cases studied.

**Conclusions:** A high proportion of familial MSI cases and a lower incidence of TP53 mutations are some of the hallmarks of the Saudi colorectal carcinomas which need to be explored further.

#### Progress

Manuscript accepted in *Saudi Medical Journal*. 2007 – In press.

#### Bortezomib (Velcade®) Induces p27Kip1 Expression through SKP2 Degradation in Colorectal Cancer

**Background:** SKP2, an F-box protein targets cell cycle regulators including cycle-dependent kinase inhibitor p27Kip1 via ubiquitin-mediated degradation. SKP2 is frequently overexpressed in variety of cancers. We investigated the role of SKP2 and its ubiquitin-proteasome pathway in colorectal carcinoma using a panel of cell lines, clinical samples and nude mouse model.

**Methods:** Cell proliferation was evaluated by MTT assay. Cell cycle distribution was evaluated by propidium iodide staining and flow cytometric analysis. The apoptosis was measured by Annexin/Propidium iodide staining and by DNA fragmentation assays. SKP2 and P27Kip1 protein expression were determined by IHC on tissue microarray setting as well as with Western blotting.

**Results:** Using immuno-histochemical analysis on a large tissue microarray of 448 samples, an inverse association of SKP2 expression with p27Kip1 protein levels was seen. CRC subset with high level of SKP2 and low level of p27Kip1 showed a decreased overall survival ( $p=0.0057$ ). Treatment of CRC cell lines with Bortezomib or expression of siRNA of SKP2 causes downregulation of SKP2 and accumulation of p27Kip1. Furthermore treatment of CRC cells with Bortezomib causes apoptosis via involving mitochondrial pathway and activation of caspases. In addition, treatment of CRC cells with Bortezomib downregulated the expression of XIAP, cIAP1 and survivin. Finally, treatment of CRC cell line xenografts with Bortezomib resulted in growth inhibition of tumors in nude mice via downregulation of SKP2 and accumulation of p27Kip1.

**Conclusions:** Altogether, our results suggest that SKP2 and ubiquitin-proteasome pathway may be a potential target for therapeutic intervention for treatment of CRC.

**Progress**

Manuscript in revision Cancer Research 2007.

**Fatty Acid Synthase Inhibition Suppresses P AKT and Triggers Apoptosis in Colorectal Cancer.**

Fatty acid Synthase (FASN) is an enzyme that plays critical role in de novo synthesis of fatty acids. FASN is over expressed in a number of human cancers but its role has not been elucidated in colorectal cancers (CRC). Using tissue microarray technology, immunohistochemistry was performed on 448 samples that show that expression of FASN is associated with activated AKT (p-AKT) in CRC. Our in vitro study show that treatment of CRC cell lines (Colo-320, HCT-15 and SW-480) with C-75, an inhibitor of FASN suppresses growth and induces apoptosis in all cell lines. Treatment of CRC cells with C-75 or expression of FASN siRNA causes down regulation of FASN and inactivation of AKT activity. However, down-regulation of AKT expression by si-RNA or in-activation of AKT by a direct inhibitor of AKT does not affect the expression of FASN. Furthermore treatment of CRC cell lines with C-75 results in apoptosis via activation of caspase-8 and truncation of Bid causing tBid translocation to the mitochondria where it causes conformational changes in Bax leading to loss of mitochondrial membrane potential and release of cytochrome c to the cytosole. Cytochrome c release leads to formation of the apoptosome in conjunction with caspase-9 and Apaf leading to activation of down-stream caspase-3 and cleavage of PARP. In addition, treatment of CRC cells with C-75 also down regulates the expression of anti-apoptotic proteins, XIAP and cIAP1. Finally, treatment of Colo-320 and HCT-15 xenografts with C-75 results in growth inhibition of tumors in Nude mice via down-regulation of FASN expression and inactivation of AKT. Our results suggest that FASN and activated AKT pathway may be a potential target for therapeutic intervention for the treatment of CRC.

**Progress**

Manuscript submitted to Gastroenterology 2007.

**OVARY**

**Investigators:** Khawla S. Al-Kuraya, Shahab Uddin, Maqbool Ahmed, Jehad Abubaker, Abdul Khalid Siraj, Prashant P. Bavi, Zeenath Jehan, Azhar R. Hussain.

**Proteasome Inhibitor Bortezomib (Velcade®) Induces Apoptosis Via Degradation Of Skp2 In Ovarian Cancer**

Ubiquitin-dependes proteolysis of cyclins plays a critical role in cell cycle progression and tumorigenesis in varieties of cancer. SKP2, an F-box protein targets cell cycle regulators including cycle-dependent kinase inhibitor p27kip1 via ubiquitin-mediated degradation. SKP2 is frequently overexpressed in variety of cancers. We investigated the role of SKP2 and its Ubiquitin Proteasome pathway in epithelial ovarian cancer using a panel of cell lines, and Nude mouse model. Treatment of epithelial ovarian cancer cell lines with Bortezomib, an inhibitor of proteasomal pathway causes downregulation of SKP2 and accumulation of p27kip1 leading to apoptosis. Bortezomib induces activation of caspase-8 and cleavage of Bid subsequently leading to loss of mitochondrial membrane potential and release of cytochrome c into cytosol, resulting in activation of caspase-3 and cleavage of PARP. In addition, treatment of epithelial ovarian cancer cells with Bortezomib downregulated the expression of XIAP, and survivin. The expression of SKP2 is suppressed by targeted knock-down with small interfering RNA. The ablation of SKP2 activity causes a dramatic down-regulation of Skp2 protein leading to upregulation of p27Kip1. In addition, we demonstrate that pretreatment of epithelial ovarian cancer cells with z-VAD-fmk, a universal inhibitor of caspases abrogates caspase and PARP activation and prevents cell death induced by Bortezomib. Finally, treatment of ovarian cancer cell line Xenograft with Bortezomib resulted in growth inhibition of tumors in Nude mice via down regulation of SKP2 and accumulation of p27kip1. Altogether, these results suggest that SKP2 and ubiquitin-proteasome pathway may be a potential target for therapeutic intervention for treatment of epithelial ovarian cancer.

**Progress**

Manuscript under preparation.

**Apoptosis Induced By Aspirin Via Inhibition Of Akt Activity And Downregulation Of Cyclooxygenase 2 Expression**

Emerging evidence supports a role for prostaglandins (PG) and their synthesizing enzyme, cyclooxygenase 2(COX2), in tumor angiogenesis. Prostaglandins are fatty-acid derivatives located all over your body that are well known for their inflammation and immune response effects. COX2 appears to be involved at various steps in the processes of tumor progression. Aspirin treatment

induced apoptosis in the epithelial ovarian cancer cells causes downregulation of constitutively active AKT and suppressed the expression of COX2. Our data demonstrates that Aspirin treatment of ovarian cells induces activation of caspase-8 and truncation of BID, subsequently loss of mitochondrial membrane potential and release of cytochrome c to the cytosol. Resulting in activation of caspase-3 and cleavage of PARP. Finally, aspirin inhibits that expression of XIAP, an anti-apoptotic protein that has been shown to regulated by AKT. Finally, treatment of ovarian cells Xenograft with Aspirin resulted in growth inhibition of tumors in Nude mice via down regulation of AKT and COX2. Taken together these results provide the molecular basis and preliminary data for new treatment strategies that may incorporate aspirin and other NSAID drugs in treatment regimens for ovarian cancer.

### Progress

Manuscript under preparation.

### FUTURE DIRECTION AND RESEARCH

The Department of Human Cancer Genomic Research will continue on our main focus "human cancer genomic research". Complementing clinical research with Basic science studies including in-vitro functional assays and in-vivo animal models will further enhance our research in the field of cancer. This combined approach will help us in detection of more important and critical genetic markers that can be used for diagnosis, prognosis or as potential targets to treat these malignancies. These studies will definitely improve the over-all survival of patients suffering from these cancers.

Within our research laboratory, we will continue using state-of-the-art approaches to study fundamental questions regarding cancer in Saudi Arabia and 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.

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**NATIONAL LABORATORY FOR  
NEWBORN SCREENING**



The

## NATIONAL LABORATORY FOR NEWBORN SCREENING

The National Laboratory for Newborn Screening (NLNBS) is both a service and research unit and is currently in contract with Prince Salman Center for Disability Research (PSCDR) and the Saudi Ministry of Health to execute Phase I of the Saudi Newborn Screening Program. The number of participating Ministry of Health hospitals has been increased to 24 during 2007. As a result, the number of newborns screened by the program increased significantly to approximately 100,000 newborns. In addition to the newborn screening, the NLNBS conducted about 400,000 specialized tests on specimens of blood, plasma, urine and CSF for follow-up of treatment or from new patients from over 200 different hospitals.

NLNBS maintains its research activities either independently or in collaboration with other KFSH&RC clinical departments and with local and international institutions. This work was translated into several important publications in international peer-reviewed journals.

### *Head, Program Management* **Ali Al-Odaib PhD**

#### **Members**

Osama Al-Dirbashi, BPharm, PhD  
(Head, Laboratory Services)  
Ayman Al-Sulaiman PhD  
Amal Saadallah, MD, PhD  
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Khaled Al-Qahtani  
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Ellena Bernabe (grant)  
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Reham Al-Khinany (grant)  
Rana Akili (grant)  
Bindhu Kumari (grant)  
Ebtessam Jambi (grant)  
Asmahan Ahmad (grant)  
Lolwa Jomaa (grant)  
Emalyn Samonte (grant)

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

The program targets 120,000 newborns from 24 major birth centers from different regions of KSA. The program includes screening dried blood spots from newborns at 24-72 hours after birth for 16 inherited metabolic and endocrine disorders (see list below).

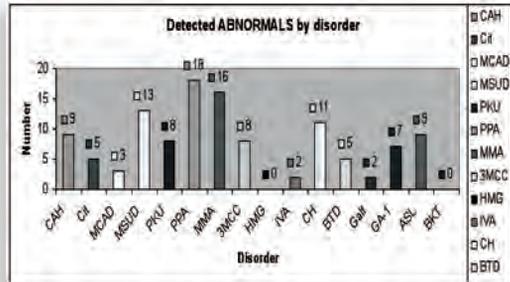
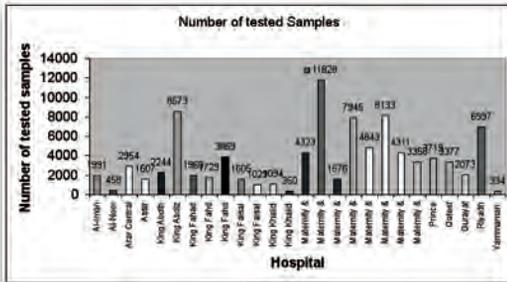
1. Phenylketonuria (PKU)
2. Maple Syrup Urine Disease (MSUD)
3. Arginosuccinase Deficiency (ASL)
4. Citrullinemia (ASD)
5. HMG-CoA Lyase Deficiency (HMG)
6. Isovaleric Acidemia (IVA)
7. Methylmalonic Acidemia (MMA)
8. Propionic Acidemia (PA)
9. Beta-ketothiolase Deficiency (BKT)
10. Methylcrotonyl-CoA 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)

The first 12 of these diseases are screened for by tandem mass spectrometry, the last 4 disorders are screened for by four different fluoroimmuno assays. The diagnosis of the detected cases are confirmed in the NLNBS utilizing various technologies such as tandem mass spectrometry, amino acid analyzer, HPLC, and moor.

**Progress**

During 2007, the total number of hospitals has increased to 24 birth centers from more than 11 provinces of the kingdom. The program is administered by Prince Salman Center for Disability Research (PSCDR) and financed and supervised by the Ministry of Health. In 2007 we managed to screen about 100,000 babies and conducted more than 500,000 deferent tests. More than 115 babies were found to be affected yield an incidence of 1:750. We are facing some logistical difficulties but this is improving gradually. We are currently working closely with the Ministry of Health to expand the program to cover the screening of 170,000 newborn during 2008. This expansion will be combined with extensive campaign for the program in the media.



**PROGRAM IN BIOMOLECULAR  
RESEARCH**



Program in

# BIOMOLECULAR RESEARCH

The ultimate goal of the research program is to focus on discovery and target validation of the molecular pathways that are perturbed as a result of disease and can be targeted by therapeutics. The research program employs the fields of functional genomics, functional proteomics, and molecular therapeutics to achieve this purpose by narrowing the human transcriptome and proteome to early and transient response players. Thus, the program is focused on the important decision making players in innate immunity, cellular growth control, and inflammatory response including interferons, cytokines, and negative feedback regulators. Specifically, the laboratory studies are aimed at the molecular pathways regulating mRNA stability in health and disease, and applying this knowledge for therapeutic purposes.

Using the unique tools developed in our program, we emphasized on the regulation of mRNA stability-mediated pathways by a number of RNA binding proteins, and the relationship of these interactions, to disease mechanisms.

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## *Director*

**Khalid S. Abu Khabar, PhD**

## *Members:*

Edward Hitti, PhD, Associate Scientist  
Anas Al-Halees, PhD, Post-Doctoral Fellow  
Latifa Al-Haj, BSc, Research Associate  
Maha Al-Ghamdi, MSc, Research Assistant  
Wijdan, Al-Ahmadi, BSc, Research Assistant  
Nora Al-Suhaibani, PhD Student  
Maher Al-Saif, BSc, Research Technician  
Mustafa Sheikh, BSc, Grant Employee  
Tala Bakheet, MSc, (on scholarship leave)  
Fahad Al-Zoghaibi, BSc, (on scholarship leave)

## RESEARCH LINES AND PROJECTS

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### **Functional genomics and proteomics of early response transcriptome (KACST- funded projects)**

The overall aim of the project is to develop functional genomics and proteomics tools specific to AU-rich elements, found in many unstable mRNAs, in order to perform genome-wide analysis of ARE-gene expression.

### **Ribonuclease L regulation of cellular mRNAs in health and disease**

The aim of this project is to understand the mechanism of the cellular growth suppression by RNase L and how RNase L mutations associated with cancer can affect this regulation.

### **Role of AU-Rich RNA binding protein, tristetraprolin in inflammation and cancer.**

The aim of this project is to study large-scale functional properties of ARE-genes as influenced by RNA binding proteins and relationship to inflammation and cancer.

### **Role of mRNA stabilization in innate immunity to viruses (NIH sub-contract)**

The aim of the consortium work is to delineate the IFN response to viruses, particularly, hepatitis C virus, and effect of chemokines and other modulators.

### **Bioinformatics of AU-rich elements**

The aim of this project is expand and update ARED database to other organisms.

### **Others**

Various international collaborative research projects on modulation of gene expression by RNA binding proteins

## FUTURE RESEARCH DIRECTION

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The program still shares the same focus and direction in the future. A large scale view and analysis of RNA stability changes during innate immunity and cellular growth will be facilitated by the various tools that were developed in the past few years. We will continue exploring the role of RNase L in regulating cellular growth and as perturbed during cancer. Large-scale functional analysis of ARE-mRNA stability in several cellular models of disease will be performed.

## PUBLICATIONS

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  - Halees AS, El-Badrawi R, Khabar KS. ARED Organism: expansion of ARED reveals AU-rich element cluster variations between human and mouse. *Nucleic Acids Res*. 2008 Jan;36(Database issue):D137-40. Epub 2007 Nov 4.
  - Ruggiero T, Trabucchi M, Ponassi M, Corte G, Chen CY, al-Haj L, Khabar KS, Briata P, Gherzi R. Identification of a set of KSRP target transcripts upregulated by PI3K-AKT signaling. *BMC Mol Biol*. 2007 Apr 16;8:28.
  - Khabar KS, Young HA. Post-transcriptional control of the interferon system. *Biochimie*. 2007 Jun-Jul;89(6-7):761-9. Epub 2007 Feb 24. Review.
  - Khabar KS. Rapid transit in the immune cells: the role of mRNA turnover regulation. *J Leukoc Biol*. 2007 Jun;81(6):1335-44. Epub 2007 Mar 30. Review.
  - Al-Zoghaibi F, Ashour T, Al-Ahmadi W, Abulleef H, Demirkaya O, Khabar KS. Bioinformatics and experimental derivation of an efficient hybrid 3' untranslated region and use in expression active linear DNA with minimum poly(A) region. *Gene*. 2007 Apr 15;391(1-2):130-9. Epub 2006 Dec 30.
  - Gherzi R, Trabucchi M, Ponassi M, Ruggiero T, Corte G, Moroni C, Chen CY, Khabar KS, Andersen JS, Briata P. The RNA-binding protein KSRP promotes decay of beta-catenin mRNA and is inactivated by PI3K-AKT signaling. *PLoS Biol*. 2006 Dec;5(1):e5.
  - Wagoner J, Austin M, Green J, Imaizumi T, Casola A, Brasier A, Khabar KS, Wakita T, Gale M Jr, Polyak SJ. Regulation of CXCL-8 (interleukin-8) induction by double-stranded RNA signaling pathways during hepatitis C virus infection. *J Virol*. 2007 Jan;81(1):309-18. Epub 2006 Oct 11.
  - Green J, Khabar KS, Koo BC, Williams BR, Polyak SJ. Stability of CXCL-8 and related AU-rich mRNAs in the context of hepatitis C virus replication *in vitro*. *J Infect Dis*. 2006 Mar 15;193(6):802-11. Epub 2006 Feb 13.
  - Bakheet T, Williams BR, Khabar KS. ARED 3.0: the large and diverse AU-rich transcriptome. *Nucleic Acids Res*. 2006 Jan 1;34 (Database issue): D111-4.
  - Al-Mohanna F, Saleh S, Parhar RS, Khabar K, Collison K. Human neutrophil gene expression profiling following xenogeneic encounter with porcine aortic endothelial cells: the occult role of neutrophils in xenograft rejection revealed. *J Leukoc Biol*. 2005 Jul;78(1):51-61. Epub 2005 Apr 4.
  - Khabar KS. The AU-rich transcriptome: more than interferons and cytokines, and its role in disease. *J Interferon Cytokine Res*. 2005 Jan;25(1):1-10. Review.
  - Khabar KS, Bakheet T, Williams BR. AU-rich transient response transcripts in the human genome: expressed sequence tag clustering and gene discovery approach. *Genomics*. 2005 Feb;85(2):165-75.
- Invited Talks and Oral Presentations:**
1. Khabar, K.S. 2008. Molecular response to therapeutic interferons: Sensitivity and resistance mechanisms. 1<sup>st</sup> International Conference On Drug Design & Discovery. Dubai. February 4-7.
  2. Khabar, K.S. 2007. Gene regulation in innate immunity and cellular growth: The Rapid Transit. Keynote Invited Speaker.
  3. A biologist view of bioinformatics: Example with early response transcriptome. Invited Speaker. 1<sup>st</sup> Saudi Bioinformatics Workshop, Riyadh.
  4. Khabar, K.S.A. 2005. A Bird's Eye View of AU-Rich Element in the Human Genome. Invited Speaker. EMBO mRNA turnover. Arolla, Switzerland.
- Patent Applications**
1. Method of generating translationally active linear DNA molecules and use thereof in array formats.
  2. Hybrid 3'-untranslated regions suitable for efficient protein expression in mammalian cell.



# **STEM CELL THERAPY PROGRAM**



The

## STEM CELL THERAPY PROGRAM

The newly established 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 cardiovascular, neurodegenerative, renal, liver, and autoimmune diseases, spinal cord injuries, diabetes and cancer. The Program will house several research groups and Core Facilities working in close collaboration towards achieving the goal of excellence in stem cell research in the Middle East area and worldwide. Members of the program are expected to actively participate in basic and clinical research, teaching, and in collaborative projects with the scientific and medical community.

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*Director*

**Chaker Adra, PhD**

*Administrative Staff*

Katharine Ritchie

## UNITS

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### Our program consists of four main units

1. Histocompatibility and Immunogenetics Research Unit
2. Tumor Immunology Research Unit
3. Flow Cytometry Core Facility Unit
4. Proteomic Research Unit (recently incorporated)

## MAJOR ACHIEVEMENTS

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During the short period since its establishment, the Stem Cell Therapy Program has determined to raise the bar for type and quality of science it carries out and services it provides. Toward this goal, we have;

- Established a new independent unit to study stem cell biology in collaboration with The Transplantation Center at Harvard Medical School.
- Signed two Memoranda of Understanding with two prestigious institutions:
  1. Harvard Medical School (USA).
  2. INSERM and University Hospital Center (France).
- Successfully recruited a world expert in Transplantation and Stem Cell Therapy, Mohamed H. Sayegh M.D., Warren E. Grupe and John P. Merrill Chair in Transplantation Medicine, Professor of Medicine and Pediatrics, Harvard Medical School, Director, Transplantation Research Center, Brigham and Women's Hospital & Children's Hospital Boston, as an Adjunct Principal Scientist with the Stem Cell Therapy Program.
- Established international collaborative projects between King Faisal Specialist Hospital and Research Centre (KFSH&RC) and Transplantation Center at Harvard Medical School, USA as well as Karolinska University Hospital, Sweden.
- Submitted two patent applications :
  1. "Granulocytes Subtype-Selective Receptors and Ions Channels and Uses thereof"
  2. "Methods and Composition for Cell-Cycle Regulation"

## OVERVIEW OF RESEARCH ACTIVITIES

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- The creation of a functional and dynamic Stem Cell Therapy Program capable of conducting translational

stem cell therapy research of high international standard.

- Secure International Accreditation for the Stem Cell Therapy Program for clinical use in collaboration with The Department of Pathology, KFSH&RC.
- Commence pilot clinical trials of stem cell therapy in the field of cardiovascular, neurodegenerative, renal, liver and autoimmune diseases, spinal cord injuries, diabetes and cancer.
- Five proposals have been submitted during the 2007 academic year:
  - Development of Autologous Stem Cell Therapy for Patients with Severe Peripheral Arterial Disease of the Lower Limbs-A Phase II Non-Randomized Study
  - Stem Cells Interactions with the Inflammatory Environment in Multiple Sclerosis and other Neurodegenerative Diseases of the Central Nervous System
  - The Propagation of Mesenchymal and Neural Stem Cells From Adult Olfactory Mucosa
  - Neurosteroids and Alzheimer Disease: Protection Against Beta-Amyloid-Induced Toxicity in Neuronal Cells
  - Identification and Therapeutic Targeting of ABCB5+ Tumor Stem Cells

Dr. Adra is involved in organizing the Juvenile Diabetes Research Foundation (JDRF) Workshop on Stem Cell Therapy in Human Diseases, reviewing scientific abstracts and papers for The American Transplant Congress (ATC) and chairing the Islet and Stem Cell Transplantation Session at the ATC, Toronto, Canada for 2008.

Within the short period of time the following abstracts have been submitted:

- Kutok Jeffrey, Yang Xing, Folkerth Rebecca, and Adra Chaker. Characterization of the Expression of the Cell Cycle Regulator HTm4 (MS4A3) in Human Peripheral Blood Cells and Normal and Malignant Tissues. International Congress on Bone Marrow and Stem Cell Transplantation, 13-15 November 2007, Riyadh, Saudi Arabia.
- Fiorina Paolo, Jurewicz Mollie, Vergani Andrea, Gebhard Thoma, Zerwes Hans-Guenter, Adra Chaker, Sayegh Mohamed, Abdi Reza, . Mobilization of Autologous Hematopoietic Stem Cells by Targeting the CXCR4-SDF-1A Axis is Associated with Prolongation of Islet Allograft Survival. International Congress on Bone Marrow and Stem Cell Transplantation, 13-15 November 2007, Riyadh, Saudi Arabia.

## Core Facility

# FLOW CYTOMETRY

Flow cytometry plays an important role in the understanding of many biological processes, due to its ability to simultaneously analyze multiple parameters on individual cells. Chemical and physical characteristics of cells which can be measured by flow cytometry include cell size, cell shape, surface membrane receptors, DNA content, nuclear antigens, intracellular Ca<sup>2+</sup>, intracellular pH, and gene expression. Flow cytometers can analyze a population of cells, at rates of 1000 to 30,000 cells per second depending on the type of flow cytometer. With state-of-the-art instrumentation, such as the FACSAria and the BD-LSR II, the facility offers 4 way high speed cell sorting and complex analytical services. By providing these services, as well as the scientific expertise necessary to effectively use this technology, the facility serves to enhance the scope and quality of scientific research performed at the Research Centre.

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### *Head*

**Chaker Adra, PhD**

### *Members*

Fadia El Bitar, PhD  
Subramanian Manogaran, BSc  
Zuha Al-Mukhalafi, BSc  
Eyad Al-Humaidan, BSc  
Zakia Shinwari, MSc



## CORE SERVICE ACTIVITIES

Flow cytometry is extremely powerful and can lend itself to a wide range of applications including, but not limited to:

- FACS Cell Sorting
- DNA cell cycle analysis
- DNA ploidy analysis
- Apoptosis
- Immunophenotyping
- Calcium kinetics
- Bacterial measurements
- GFP measurements
- Intracellular antigen measurement
- Cytokine detection
- Platelet analysis
- Cell proliferation assays
- Cellular viability
- Data analysis and data interpretation

The following statistics illustrate the nature and volume of samples handled by the facility as an average in a period of one month.

TYPE OF SERVICE PROVIDED	SERVICE RECIPIENT (Department/University)	VOLUME (i.e., number of samples processed)
Cell Separation	KFSH&RC	20 samples/month
DNA Cell cycle Analysis	KFSH&RC	280 samples/month
Immuno-phenotyping	KFSH&RC	200 samples/month
Cell Viability	KFSH&RC	150 samples/month
Calcium signaling	KFSH&RC	10 samples/month
Apoptosis	KFSH&RC	300 samples/month
Intracellular Staining	KFSH&RC	25 samples/month

## CORE RESEARCH ACTIVITIES

**Project title: Flow Cytometric Analysis of Minimum Residual Disease in Paediatric Acute Lymphoblastic Leukaemia at KFSHRC. RAC #: 2001 007**

**Investigators:** Dr. Abdallah Al-Nassar, Dr. Tariq Al-Asaad, Dr. Khaled Al-Hussein, Dr. Hassan El Solh, Dr. Hassan El Bushra

### Project description

Almost all children who are treated for acute lymphocytic leukemia (ALL) enter complete remission. However, nearly one fourth of these patients subsequently experience relapse and have a poor prognosis. Many relapses may be preventable if at-risk patients can be identified early and given more intensive therapy. The study of minimal residual disease (MRD) is an attempt to detect and define the significance of leukemia invisible to normal morphologic examination. MRD is closely related to the risk of relapse during all the course of chemotherapy and can be used as a prognostic factor as soon as induction therapy is completed. The risk of relapse rises steeply with the amount of residual blasts, and the extent of MRD predict the outcome more precisely than simple presence or absence. Using rapid flow-cytometric techniques capable of detecting one leukemic cell in 10000 normal cells, we are studying MRD in children with ALL in first clinical remission after 28 or 43 days of treatment.

### Progress

On going.

**Project title: P-Glycoprotein in Childhood Acute Leukemia in KSA: A Prospective Study of Expression and Correlation with Outcome. RAC#: 2001 004**

**Investigators:** Dr. Abdallah Al-Nassar, Dr. Khaled Al-Hussein, Dr. Abdullah Baothman, Dr. Hassan El Solh, Dr. Hassan El Bushra

### Project description

One of the mechanisms leading to relapse in childhood acute leukemias is thought to be emergence of multi drug resistance. The expression of Multi-Drug Resistance phenotype is a key determinant in the development of therapeutic and chemotherapeutic drugs. For many

novel compounds the accessibility, solubility, clearance rate and drug-drug interactions can mean the difference between a wonder drug and a lethal drug. The classical form of multi-drug resistance hinges on the presence of P-glycoprotein (Pgp) structure at the cell membrane. Pgp acts as a drug efflux pump, thus providing a system to rid cells of both toxic and therapeutic compounds. Flow cytometry is particularly useful to monitor MDR level not only in leukemic patients with resistant or relapsed disease but also in some patient at diagnosis and in complete remission.

#### Progress

On going.

**Project title: Study of the Tumor Suppressor Genes in DNA Repair and Cell Cycle Checkpoints. RAC #: 990025**

**Investigators:** Dr. Abdelilah Aboussekhra, Dr. Mai Al-Mohanna, Dr. Khaled Al-Hussein

#### Project description

Alteration in the genes that encode DNA cell cycle regulation and DNA repair leads to neoplasm. Therefore, understanding the genes that play role in DNA repair and cell cycle check points helps in the prevention of Cancer. Flow cytometry plays an important role to study the genes which control the DNA cell cycle.

#### Progress

On going.

**Project title: Role of Novel Compound from Plant, Marine and Microbial Sources in the Breast Cancer Chemoprevention. RAC #: 2030041**

**Investigators:** Dr. Fahad Al-Khodairy, Dr. Arif Jamal, Dr. Malibari, Kunhi, Muhammad

#### Project description

Plant extracts have been used for ages to cure various ailments. Drugs such as Vinblastine, purified from plant extract (*Vinca rosea Linn*) found to be useful as anti cancer drug. Flow cytometry is utilised for monitoring cell cycle, apoptosis and cytotoxicity of plant extracts in various cell lines as well as cells isolated from fresh tissues.

#### Progress

On going.

**Project Title: Towards the Understanding of Sperm Role in Fertilization and Early Embryonic Development: A pilot Study. RAC #: 2040040**

**Investigators:** Dr. Namik Kaya, Dr. Ali Hellani

#### Project description

Male factor infertility is common in patients undergoing infertility treatment in our hospital. Many of such cases have unexplained in nature and patients were treated without knowing the reason why they are infertile. A recent study suggested that sperm delivers not only DNA but also RNA to the oocytes. In this pilot study, Spermatozoa from a total of 100 patients will be screened for the level of 6mRNAs that have been pointed out to have role on fertilization and early embryonic development. Their level will be correlated to the outcomes of the treatment. Flow Cytometry will play an important role to detect apoptotic sperm.

#### Progress

On going.

**Project title: BC/ABL Translocation Status and T-Cell Stimulation Capacity of Dendritic Cells Derived from CD34+ and CD34-Bone Marrow Compartments from Patients with Myeloid Leukaemia. AC #: 990029**

**Investigators:** Dr. Hamad Al-Omar, Dr. Khaled Al-Hussein, Dr. Mahmoud Al-Jurf, Dr. Anwar Iqbal, Dr. Abdelghai Tbakhi

#### Project description

Treatment of relapsing hematological malignancies specially chronic myeloid leukemia after bone marrow transplantation with adoptive immunotherapy utilizing donor leukocyte infusions is effective. However it can lead to graft versus host disease(GVHD).Dendritic cells (DC) are potent and professional antigen presenting cells, and activate naive T-cells with specific antileukemia activity which provide a model for immunotherapy and avoids side effects particularly GVHD. Dendritic cells from chronic myeloid leukemia (CML) demonstrated a lower capacity of T-cell stimulation compared to DC from normal subjects. CD34 -/ lineage cells, could represent earlier stem

cells compared to CD34+/lineage cells. These cells may have higher proportions of bcr/abl-negative cells that might have a better antigen presentation capacity. Flow cytometry will play an important role to understand whether DC from CD34 - / lineage compartment carry the bcr/abl translocation and also their capacity as antigen presenting cells.

#### Progress

On going.

**Project title: Evaluation of Anti-tumour Activity of  $\lambda\delta$  T-cells in Cancer Patients. RAC #: 2030 022**

**Investigators:** Dr. Khaled Al-Hussein, Dr. Mahmoud Al-Jurf, Dr. Shoukri Bazarbashi, Dr. Abdelghani Tbakhi, Dr. Ahmed Al-Omar

#### Project description

The  $\lambda\delta$  T-cells play important role in immunological control against malignancies. In recent review, reports have shown that preferential expansion of  $\gamma\delta$  T-cells in certain malignancies supports a possible role of these cells in immunological surveillance against cancer. *In vitro* studies have demonstrated that peripheral  $\gamma\delta$  T-cells of healthy donors similarly have several fold greater cytolytic activity in various tumor cell lines. In this project, Flow cytometry will be used to study the direct role of  $\gamma\delta$  T-cells in tumor elimination by studying their cytotoxic effect and the intracellular cytokines they produce in cancer patients and also to evaluate the  $\gamma\delta$  T-cells functions whether they are deficient in different cancer patients in comparison with healthy donors.

#### Progress

On going.

**Project title: Neuroactive Steroids and Alzheimer's Disease: Protection Against  $\beta$ -Amyloid Peptide-Induced Toxicity in Neuronal Cells**

**Investigators:** Dr Fadia El Bitar; Dr Yvette Akwa; Dr Chaker Adra

#### Project description

An increasing body of evidence indicates that the neurotoxicity of  $\beta$ -amyloid (A $\beta$ ) protein plays a key role in

the pathological events occurring in Alzheimer's disease. Our work focuses on examining the potential neurotrophic and neuroprotective effect of specific neurosteroids against the neurotoxicity induced by A $\beta$ 1-42 peptide, using rat neuroblastoma B104 as cell culture model.

#### Progress

Our current results show that PREGS exhibit striking neurotrophic effects on B104 cells in culture. This neuronal outgrowth has been demonstrated clearly by immunocytochemistry using the neuronal marker anti-68KDa neurofilament protein fluorescent antibody. The rate of apoptosis that reflects the neurotoxic effect of A $\beta$  peptide and the potential neuroprotective effect of steroids are currently under investigation on B104 cells, by using flow cytometry. Preliminary results show that A $\beta$ 1-42 peptide induces the necrosis of B104 cells. Additional experiments are now planned in order to observe the potential neuroprotective effect of steroids against the necrotic action of A $\beta$ 1-42 peptide.

Overall, the novel strategy used in our study, using specific neuroactive steroids that may counteract the neurotoxic effects of A $\beta$  peptide is promising.

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#### FUTURE RESEARCH DIRECTION

The recent addition of BD FACSAria™ and BD-LSR II, the state-of-the art instruments, will certainly facilitate our goal to render the best service to wide range users at the Research Centre. The aim of the facility is to complement the cutting-edge research into molecular, cellular and developmental biology of mammalian stem cells by providing a comprehensive service in technologies relating to cell sorting and analysis.

We have plan to strengthen our cell sorting capability with MACS sorting using dedicated magnetic sorter from Miltenyibiotec. We have also plan to introduce Laser Scanning Cytometry (LSC), from CompuCyte. This laser scanning cytometer (LSC) allows flow cytometric analysis of cells fixed to a microscope slide. This unique instrument platform allows cytometric scatter and fluorescence measurement on adherent T-cells where removal for traditional flow analysis would disrupt the phenotype (particularly for physiological assays such as apoptosis, plasma membrane or mitochondrial membrane potential, etc.)

## PUBLICATIONS

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### Peer Reviewed Articles

- Hussain AR, Al-Jomah NA, Siraj AK, Manogaran P, Al-Hussein K, Abubaker J, Platanius LC, Al-Kuraya KS, Uddin S. Dependent Induction Of Apoptosis In Primary Effusion Lymphoma Cells. *Cancer Research*. 2007 Apr 15;67(8):3888-97.
- Shinwari Z, Manogaran PS, Alrokayan SA, Al-Hussein KA, Aboussekhra A. Vincristine and Iomustine Induce Apoptosis and p21(WAF1) Up-regulation in Medulloblastoma and Normal Human Epithelial and Fibroblast-cells. *J Neurooncol*. 2007 Dec 6; [Epub ahead of print]
- Jamal M.Arif, Mohammed Kunhi, Manogaran P. Subramanian, Adnan A. Bekhit, Ola A. El-Sayed, Khaled Al-Hussein, Hassan Y. Aboul-Enein, Fahad M. Al-Khodairy. Cytotoxic and Genotoxic Potentials of newly Synthesized Antiviral Aminopyrazoloquinoline Derivatives. *Medical Chemistry Research*. Accepted Nov 2007.
- Mammo L, Sheereen A, Saour T, Shoukri M, Saour J. Incidence of Five Prothrombotic Gene Polymorphisms in Healthy Saudi Arabians. *Journal of Thrombosis and Haemostasis*. 2007; 5:877-878.

### Abstracts

- Saour J, Sheereen A, Mammo L. The 4G/5G Insertion/Deletion Polymorphism of the Plasminogen Activator Inhibitor-1 Gene is Associated with Venous Thrombosis. *Journal of Thrombosis and Haemostasis* 2007:5 Supplement 2: P-S-359.



## Research Unit

# HISTOCOMPATIBILITY & IMMUNOGENETICS RESEARCH

The immune response plays a critical role in various diseases and therapies; including organ transplantation, autoimmune diseases, cancer and infectious diseases. This response is under the control of different molecules such as Human Leukocyte Antigens (HLA), NK cells immunoglobulin-like receptors (KIR) and Cytokines molecules. These molecules are of great interest because of their high polymorphism, predominant expression and ability to mount an immune response. The competence of these molecules to recognize different (self and non-self) antigens explains: organ rejection, and their critical roles in the development of autoimmune diseases, as well as cancer and infectious diseases. The mission of the Histocompatibility and Immunogenetics Research (H&I) research unit is to elucidate fundamental molecular mechanisms and cellular processes that control immune responses, in order to increase the understanding of how these genes function and to apply this knowledge to improve current therapies by tailoring the treatment of individuals based on their genetic background.

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### *Head*

**Khaled Al-Hussein, PhD**

### *Members*

Ameera Gaafar, PhD

Atia Sheereen, PhD (Grant Employee)

Abdullah Al-Sulaiman, BSc

Alia Iqniebi, BSc (Grant Employee)

In close collaboration with clinicians and scientists of the KFSH&RC and with the IHWG and SBT team from University of Utrecht, Netherlands, the section is focusing on:

- Initial determination of the frequencies of HLA class I and II alleles in the Saudi Arabian population in order to define novel alleles to explore their genetic polymorphisms for anthropological studies.
- Understanding the immunobiology and genetics of HLA polymorphisms, cytokine and KIR molecules, and their role in the immunogenetics of hematopoietic stem cell transplantation and renal allograft rejection that leads to engraftment and organ rejection.
- Genetic alteration of HLA molecules and assessing their abnormalities in malignant T-cells.
- Investigating of HLA-associated diseases such as autoimmune diseases (RA, BD and IDDM) and infectious diseases.
- Establishment of Saudi HLA genome database.

**Project title: Determination of the Effect(s) of Polymorphism(s) in Specific Genes Controlling the Immune Responses in Saudi Renal Transplant Patients. RAC # 2041081 (KACST: AT 25-41).**

**Investigators:** Khalid Al Meshari, Abdelghani Tabakhi, Khaled Al-Hussein, Ameera Gaafar

#### 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

KIR distribution was genotyped and compared between 30-kidney transplant donors and 30 recipients. All had their DNA extracted and typed using Sequence Specific Primers (SSP) technique for the presence of the different KIR loci. In agreement with published data,

we observed the dominance of the two framework genes 3DL2 and 3DL3 present in all (100%) recipients and donors investigated thus far. Other KIR genes vary in their frequencies. Moreover, the allelic distribution of all polymorphisms in the Saudi population was very similar to, the geographically and historically closest population in the Middle East, the Lebanese and the Palestinians populations. In addition, genotypic polymorphisms within genes encoding IFN- $\gamma$ , TGF- $\beta$ , TNF- $\alpha$ , IL-6 and IL-10 in a sample of 27 donor/ recipient pairs was surveyed. Currently 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 once all the samples are examined.

**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 #: 2051001 (KACST: AT- 26-03).**

**Investigators:** Mahamoud Al- Jurf, Abdelghani Tabakhi, Khaled Al-Hussein, Ameera Gaafar

#### Project description

Natural killer (NK) cells can mediate the acute rejection of bone marrow cell (BMC) allograft. 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

To date 45 healthy donor and 6 bone marrow transplant recipient samples have been screened. Whole blood was used to isolate genomic DNA. The method for typing the KIR genes was standardized. DNA typing was

carried out using the Sequence Specific Primer (SSP) technique for the presence of different KIR loci. Similar to published data, we observed that the framework genes 2DL3, 2DL4 and 3DL3 were expressed in all (100 %) recipients, whereas 2DL4, 3DL2 and 3DL3 were expressed in all (100%) donors. While other genes varied in their frequencies, 2DS5, the activating KIR gene, was not expressed by recipients. Currently few samples have been typed. Thus it is difficult to present the exact scenario of the distribution of genes in the Saudi population. Collection of more blood samples from the clinic is needed to analyze the distribution pattern of KIR genes in the Saudi population and to understand the effect of HLA mismatching in relation to KIR. Based on preliminary results, further studies are currently underway.

**Project title: Evaluation of Anti-Tumor Activity of  $\gamma\delta$  T-cells in Cancer Patients. RAC #: 2030022**

**Investigators:** Mahmoud Al-Jurf, Khaled Al-Hussein, Abdelghani Tbakhi, Hamad Al-Omar, Adher Al-Sayed, Ameer Gaafar

#### Project description

The  $\gamma\delta$  T-cells play an important role in innate and adaptive anti-tumor immunity. Most of these responses had been ascribed to  $V\gamma9V\delta2$  cells, which represent the major subset of the circulating  $\gamma\delta$  T-cells in healthy humans (1-10%). In this study, we hypothesized that paucity in  $\gamma\delta$  T-cell frequency and immune function could be related to the development of breast cancer. Ex-vivo expansion of  $\gamma\delta$  T-cells by zoledronic acid may possibly amend this deficiency. Furthermore, the granzyme B gene was screened for a known single nucleotide polymorphism.

#### Progress

The anti-tumor immune function of  $\gamma\delta$  T-cells, the granzyme B and perforin genes were screened in 30 newly diagnosed breast cancer patients and 73 normal controls. The frequency and the function of  $\gamma\delta$  T-cells were found to be reduced in peripheral blood mononuclear cells (PBMC) of breast cancer patients compared with normal donors. In addition, resting  $\gamma\delta$  T-cells from breast cancer patients produced significantly more IL-6 and TNF- $\alpha$  than normal controls. Ex vivo stimulation of  $\gamma\delta$  T-cells with zoledronic acid and IL-2 compensated, in part, for this deficiency, as they stimulated proliferation, cytokine production and enhanced the expression of granzyme B mRNA. Interestingly, when the known

Granzyme B gene polymorphism was screened, we found the prevalence of the mutated genotype RAH/RAH to be significantly ( $P < 0.017$ ) associated with breast cancer patients (14.30%) compared with normal donors (1.40%). Cytotoxicity exerted by  $\gamma\delta$  T-cells on the tumor cell lines daudi and MCF-7 were significantly higher in donors with the wild-type QPY/QPY (50%) compared with donors with RAH/RAH (21%). Our data suggests that reduction in the percentages of  $\gamma\delta$  T-cells, in addition to granzyme B gene polymorphism, leads to defective immune function in breast cancer patients. Treatment with zoledronic acid partially amends this fault. Further studies of  $\gamma\delta$  T-cell function and Granzyme B gene polymorphism in cancers, as well as the potential therapeutic use of zoledronic acid are warranted.

**Project title: BCR/ABL Translocation Status and T-cell Stimulation Capacity of Dendritic Cells Derived From CD34+ and CD34- Bone Marrow Compartments in Patients with Chronic Myeloid Leukemia. RAC#: 990 029**

**Investigators:** Hamad Al-Omar, Khaled Al-Hussein, Ameer Gaafar, Mahmoud Al-Jurf, Abdelghani Tbakhi

#### Project description

Dendritic cells (DCs) can induce immunostimulatory as well as immunoregulatory responses. This double function has made them targets for vaccine development in cancer and infection. In the present study we examined a subpopulation of DCs generated *in vitro* from CD34-/lineage-negative cells, and compared them with DCs generated from CD34+/lineage negative. Both lineages were obtained from bone marrow (BM) of patients with chronic myeloid leukemia (CML). DCs generated from normal BM donors served as controls.

#### Progress

DCs differentiated from myeloid leukemic blasts were utilized to generate cellular vaccines, as they were found to present a cluster of endogenously expressed leukemia antigens to the immune cells. CD34+ cells are known to give rise to DCs of different heterogeneity. CD34-/lineage-cells are also known to generate multilineage hematopoiesis. The status of DCs derived from CD34-/lineage-cells in regards to clonality is yet unknown. A cocktail of different cytokines {GM-CSF, TNF- $\alpha$  and IL-4} were used to generate the DCs. The DCs derived from both BM compartments, differentiated and matured similarly in culture. They expressed variable DC surface

molecules such as CD86, CD80, CD83, CD40 and HLA-DR. They stimulated allogenic T-cells when tested in a mixed lymphocytes reaction (MLR) and carried the bcr/abl fusion gene as revealed by florescence *in situ* hybridization (FISH). Our study shows that DCs generated from CD34-/lineage-cells are as potent and efficient as antigen presenting cells as those differentiated from BM CD34+/lineage-cells. In conclusion CD34-/lineage-hematopoietic BM progenitor cells can be utilized to generate DCs and hold promises in immunotherapy modality.

**Project title: Identification of HLA Alleles in Normal Saudi Individuals by Sequence Based Typing. RAC#: 2010002**

**Investigators:** Khaled Al-Hussein, 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. In this KACST approved project, 1000 healthy Saudi individuals from various regions of the Kingdom of Saudi Arabia will be HLA typed using a valuable method known as Sequence Based Typing (SBT) whereby a spectrum of HLA Class I and II alleles will be identified. This will facilitate the establishment of a Saudi HLA allele database.

#### Progress

We have studied the frequency of HLA Class I (-A, -B, -C) alleles in 100 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, Mohammed Al-Ahmed.

#### Project description

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.

#### Progress

In this project, we used a larger cohort of control subjects and patients to confirm the abovementioned hypothesis that protective HLA class II genes can override the risk provided by HLA-DQ susceptibility alleles.

**Project title: Study of the Association between HLA-DRB1 Alleles and Vogt-koyanagi-Harada's Disease in Saudi Patients. RAC #: 2050034.**

**Investigators:** Khaled Al-Hussein and Khaled Tabbara

#### 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 autoimmune 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. In Saudi Arabia, there have been no studies on the genetic predisposition among patients with VKH disease. Since VKH is common in Saudi Arabia, understanding the genetic predisposition of patients with VKH is highly desirable. Therefore, the purpose of this study was to investigate the association of HLA-DRB1 alleles with VKH patients in Saudi Arabia.

### Conclusions

Vogt-Koyanagi-Harada is associated with HLA-DRB1 \*0405. Patients with VKH, in Saudi Arabia may have genetic predisposition to environmental triggers that precipitate the clinical manifestations.

### FUTURE RESEARCH DIRECTION

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The Unit will continue its commitment towards the completion of current projects.

## PUBLICATIONS

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### Abstracts

- Gaafar A, Al-sulaiman A, Iqniebi A, Pulicat M, Al-Sayed A, Ajarim D., Chaudri, Mohareb F, Tabakhi A, Aljurf M, Al-Hussein K. Defective  $\gamma\delta$  T-cells Function and Granzyme B Gene Polymorphism Uncovered in a Cohort of Newly Diagnosed Breast Cancer Patients. *Experimental Hematology*. 2007; 35, 9 supplement 2 P040.
- Gaafar A, Al-Omar HM, Almukhlafi Z, Al-Sulaiman A, Iqniebi A, Tabakhi. A and Al-Hussein K, BCR/ ABL Translocation Status and T-cells Stimulation Capacity of Dendritic Cells Derived from CD34+ and CD34- Bone Marrow Compartments from Patients with Chronic Myeloid Leukemia. *Experimental Hematology*. 2007; 35, 9 supplement 2 P093.
- Tabbara K, Al Hussein K, Al Suliman A, Iqniebi A., HLA-DRB1 Alleles Vogt-Koyanagi-Harada VKH Disease in Saudi Arabia. *Association for Research in Vision and Ophthalmology*.



## Research Unit

# TUMOR IMMUNOLOGY

The Tumor Immunology Unit is a research facility established in 2003 to carry out research in the areas of cancer immunology and immunomodulation.

The Tumor Immunology Major Interests are:

1. **Cancer Vaccination:** To discover novel tumor antigens expressed in cancer patients in order to develop cancer vaccines for breast cancer and leukemia patients.
  2. **Immune Regulation in Cancer:** To investigate the effect of immunosuppressive molecules, such as B7-H1 and PD-1, and regulatory T-cells on the immune response of breast cancer and leukemia patients and to develop immune-based therapeutics to block their immunosuppressive effect in these patients.
  3. To design and carry out immune-based therapeutic clinical trials (B7-H1 blocking antibody, regulatory T-cells depletion, cancer vaccine).
  4. Development and/or standardization of reliable and sensitive assays to monitor immune responses in cancer patients.
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### *Head*

**Said Dermime, PhD**

### *Members*

Hazem Ghebeh, PhD

Monther Al-Alwan, PhD

Mahmoud Aljurf, MD (Adjunct position, Adult Haematology, Cancer Centre, KFSH&RC)

Faten Al-Zamel, PhD (Adjunct Scientist, King Saud University)

Cynthia Lehe, MSc

Muna Negash, Diploma (Grant, supported by KACST for 1 year & ASTF for 2 years)

Eman Barhoush, Diploma (Grant, supported by KACST for 3 years)

Ghofran Al-Qudaihi, MSc (PhD Student)

Basmah Al-Maarik, BSc (MSc student)

Khlood Al Saud, BSc (MSc student)

## RESEARCH PROJECTS

	Title of Project	Role	RAC #	Funding Agency	End of the project
1	Use of Human Dendritic Cells as Potential Adjuvant for the Generation of Specific Immune Responses to the Tumor-Associated Antigen Wilms Tumor (WT1) in the Saudi and Middle East Populations	PI	2030 006	KFSH&RC	September 2008
2	Investigation of the B7-H1 molecule expression by breast cancer and myeloid dendritic cells of Saudi breast cancer patients and blockade of the molecule as an approach for cancer immunotherapy	PI	2030 034	KFSH&RC	September 2008
3	Investigation of M-Phase Phosphoprotein (MPP11) as a Novel Target for Leukaemia T-cell Immunotherapy	PI	2040 010	KFSH&RC	September 2008
4	The Use of ELISpot Assay as a Novel Technique for Greater Accuracy and Rapid Diagnosis of <i>Mycobacterium Tuberculosis</i>	PI	2040 005	KFSH&RC	September 2007
5	The Use of Tumor-Derived RNA, Transfected in Human DCs, to Generate Breast Cancer Specific T-Cells in Saudi Women	Co-PI	Joint-Grant Granted 300,000 SR	KACST	September 2008
6	Enhancing the Immunogenicity of Low-Affinity HLA-A2 Wilms Tumor-Restricted CTL Epitopes by Selective Amino Acid Replacements: Implication in the Generation of Effective Cancer Vaccines and Adoptive T Lymphocyte Therapy in Leukemias and Breast Cancer in the Saudi Population	PI	Limited-Grant Granted 95,000 SR	KACST	September 2007
7	Investigation of the Leukemia-Associated Antigen Proteinase 3 (PR-3) as a Target for Leukemia Specific Immune Responses in the Saudi and Middle East Populations	PI	International Grant , Granted (\$35,000 for 2 years)	ASTF	February 2009
8	Investigating the Role of the Actin Bundling Protein (fascin) in Regulating Dendritic Cell Migration and Breast Cancer Metastasis in Saudi population	Co-PI	2060 016	KFSH&RC	November 2009

## PROGRESS AND RECENT FINDINGS

**Project title:** Use of Human Dendritic Cells as Potential Adjuvant for the Generation of Specific Immune Responses to the Tumor-Associated Antigen Wilms Tumor (WT1) in the Saudi and Middle East Populations.  
**RAC#:** 2030 006

**Investigators:** Said Dermime (PI), Mahmoud Al-Jurf, and Khaled Al-Hussein

## Project description

Compelling evidences indicate a key role for regulatory T-cells ( $T_{regs}$ ) in the host response to cancer. However, little is known about the antigen specificity of  $T_{regs}$ . The WT1 antigen is overexpressed in breast cancer and several human leukemias and thus considered a promising target for the development of a cancer vaccine. However, recent studies indicate that the generation of effective WT1-specific cytotoxic T-cells could be largely affected by the presence of  $T_{regs}$ .

## Progress

We were the first group to discover a T regulatory population against the WT1 antigen. We used a pool of 110 peptides across the entire WT1 protein to generate a T-cell line and clones that specifically recognized a WT1<sub>333-347</sub> (RYFKLSHLQMHSRKH) peptide (WT1-84) in an HLA DRB1\*0402/TCR-V $\beta$ 8-restricted manner. Importantly, they recognized HLA-DRB1\*04 matched fresh leukemic cells expressing the WT1 antigen. These clones exerted a Th2 (GM-CSF/IL-4/IL-5) cytokine profile, had a CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup>GITR<sup>+</sup>CD127<sup>-</sup> T<sub>regs</sub> phenotype, and possessed a strong inhibitory effect in an allogeneic MLR through a cell-contact-independent mechanism. Moreover, these clones specifically produced Granzyme B after stimulation with WT1-84 peptide or DR4-matched leukemia, and selectively induced apoptosis in WT1-84 pulsed-autologous LCL but not in DR4-matched fresh leukemic cells. These findings have important implications for the clinical manipulation of T<sub>regs</sub>, which

may have an intense impact on the inhibition of T-cell responses against leukemia. A manuscript entitled "Human CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> T<sub>regs</sub> specifically recognized an immunodominant peptide derived from the WT1 antigen expressed in leukemic cells: Implications for immunotherapy" has been submitted to *Cancer Research* and is now in revision and a poster was presented at the 1<sup>st</sup> Joint Meeting of European National Societies of Immunology Congress, Palais des Congress, Paris, France, (6-9 September 2006) and also at the World Immune Regulation Meeting "Special Focus on Regulatory Cells" 11-15 April 2007, Davos, Switzerland.

**Project title: Investigation of the B7-H1 Molecule Expression by Breast Cancer and Myeloid Dendritic Cells of Saudi breast Cancer Patients and Blockade of the Molecule as an Approach for Cancer Immunotherapy. RAC#: 2030 034**

**Investigators:** Said Dermime (PI), Taher Al-Tweigeri (PI), Hazem Ghebeh, Saud Bin Amer, Asma Tulbah, Amal Gattan, Cynthia Lehe, and Mohammad Al-Shabana

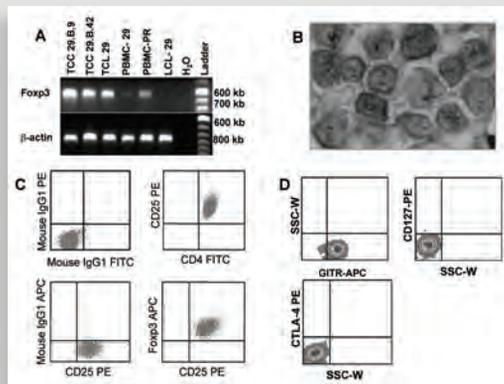
## Project description

B7-H1 is a recently identified member of the B7 family molecules. It inhibits the activation of T-cells where it protects the body from the attack by auto-reactive T-cells. B7-H1 has been detected in many cancers including lung, ovary and colon leading to immune escape of cancer cells. The aim of this project is to study B7-H1 expression in breast cancer.

## Progress

We were the first group to provide direct evidence for the association between B7-H1 expression and proliferation in breast cancer patients. (A manuscript entitled: "Expression of B7-H1 in breast cancer patients is strongly associated with high proliferative Ki-67-expressing tumor cells" was published in the *International Journal of Cancer*, 2007). A poster was presented at the 25<sup>th</sup> Congress of the International Association for Breast Cancer Research held in September 15-18, 2006 in Montreal, Quebec, Canada and published in the journal, *Breast Disease* 2006; 25: 67.

The involvement of B7-H1, PD-1 and Foxp3 molecules in the immune escape of breast cancer. B7-H1 is an inhibitory molecule that binds to PD-1 on T lymphocytes, while Foxp3 is a marker for regulatory T-cells (T<sub>regs</sub>). We have previously demonstrated the association of B7-H1-



**FIGURE 1. Phenotypic analysis of the TLC 29 T-cell line and the expanded T-cell clones generated against WT1-Pepmix. (A)** RNA expression of Foxp3 in the T-cell line (TCL 29) and clones (TCC 29.B.9, TCC 29.B.42). PBMCs from a 7-months pregnant woman (PBMC-PR) and LCL-29 was used as a positive and negative control. PBMC-29 from which the TLC 29 was generated was used as a baseline.  $\beta$ -Actin acts as a house-keeping gene. Total RNA was isolated from different individual cell types and analyzed by RT-PCR. **(B)** Cytospin immunocytochemistry double-staining of a representative T-cell clone (TCC 29.B.9) after more than 1 month in culture showing the nuclear expression of the Foxp3 protein and the membranous expression of the CD3 T-cell marker. Magnification at X520. **(C, D)** FACS analysis of a representative T-cell clone (TCC 29.B.9) showing a T<sub>regs</sub> phenotype after more than 1 month in culture.

expressing T infiltrating lymphocytes (TIL) with high-risk breast cancer patients (Ghebeh et al, Neoplasia 2006; 8: 190-198) while other studies reported the involvement of Foxp3+ T<sub>regs</sub> as a bad prognostic factor in breast tumors. Although the interaction between the two types of cells has been demonstrated *in vitro* and in animal models, their co-existence in cancer patients has not been reported. Therefore, we investigated TIL-expressing the B7-H1, PD-1, and Foxp3 molecules in tissues from 62 breast cancer patients. Tumor sections were co-stained for these molecules and their expression was correlated with factors known to be involved in the progression of the disease. A co-existence of B7-H1+ T lymphocytes and Foxp3+ T<sub>regs</sub> was evidenced by the highly significant correlation of these molecules ( $P < 0.0001$ ) and their expression by different T lymphocyte subsets was clearly demonstrated. Interestingly, concomitant presence of Foxp3+ T<sub>regs</sub>, B7-H1+ and PD-1+ TIL synergistically correlated with high histological grade (III) ( $P < 0.001$ ), estrogen receptor negative status ( $P = 0.017$ ), and the presence of severe lymphocytic infiltration ( $P = 0.022$ ). Accumulation of TIL-expressing such inhibitory molecules may deteriorate the immunity of high-risk breast cancer patients. This should encourage vigorous combinatorial immunotherapeutic approaches targeting T<sub>regs</sub> and B7-H1/PD-1 molecules in breast cancer patients. A

manuscript entitled "Foxp3+ T<sub>regs</sub> and B7-H1+/PD-1+ T lymphocytes co-infiltrate the tumor tissues of high-risk breast cancer patients: Implication for immunotherapy" has recently been published in *BMC Cancer* 2008.

**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**

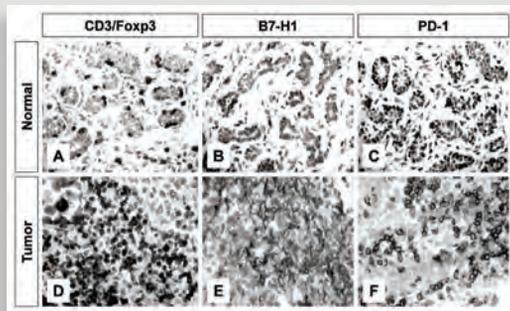
**Investigators:** Monther Alwan (PI), Said Dermime (PI), Hazem Ghebeh, Asma Tulbah, Taher Al-Tweigiri, Dahish Ajarim, Mahmoud Al-Jurf

#### Project description

This proposed study is the first to examine whether fascin expression in breast cancer cells is directly responsible for mediating tumor metastasis. Gain and loss of functions are used *in vitro* using known breast cancer cell lines. In addition, retrospective study will be done on *in vivo* paraffin embedded samples

#### Progress

Both *in vivo* and *in vitro* approaches were utilized to address the project hypotheses. Several breast cancer cell lines were used to examine fascin function *in vitro*. This approach gave us the opportunity to manipulate fascin expression and study its effect in breast cancer. First, the protocol for the detection of fascin by flow cytometry and immunohistochemistry was optimized. Among the breast cancer cell lines that tested, MDA-MB-231 expressed the highest level of fascin, while T47D was fascin negative and MCF-7 expressed low to moderate level of fascin (Figure 3). To address the role of fascin *in vitro*, EGFP-fascin cDNAs were delivered into the fascin-negative T47D cell lines using the novel Nucleofector technology (developed by Amaxa Biosystems) for highly efficient gene transfer into primary cells or hard-to-transfect cell lines. Wild type (WT) and mutants (S39A and S39D) of EGFP-fascin cDNA were generated and their purities were confirmed using fascin specific primers. The conditions for fascin delivery into the human breast cancer cell lines were optimized such as DNA concentration, cell number, cell viability, incubation time and transfection efficiency. Stable clones were obtained after selection with G418 for 4 weeks (Figure 4).



**FIGURE 2. Immunohistochemical staining of Foxp3+ T<sub>regs</sub>, B7-H1+ and PD-1+ in T lymphocytes of breast tissues.** Representative micrographs at X530 magnification of [A&D] CD3/Foxp3 double staining, [B&E] B7-H1 staining, [C&F] PD-1 staining. Upper panel [A-C] is sections for breast duct and lower panel [D-F] is sections for infiltrating ductal carcinoma of the breast.

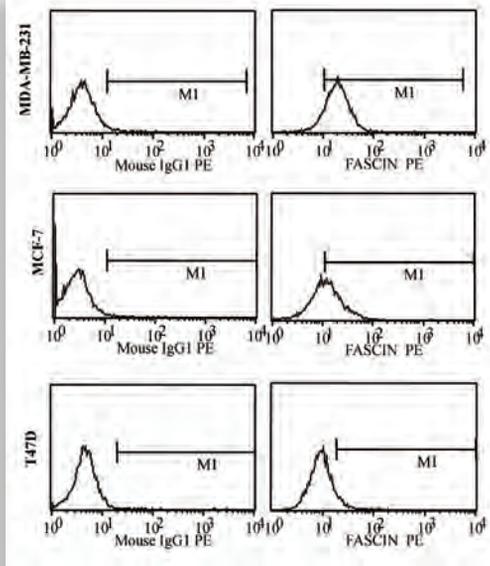


FIGURE 3. Fascin expression in breast cancer cell lines.

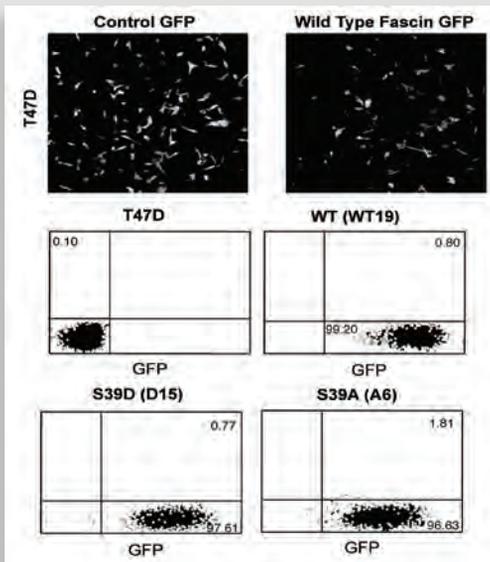


FIGURE 4. Stable clones of T47D cell line after GFP-Fascin transfection and G418 selection.

## FUTURE RESEARCH DIRECTION

We will continue to carry out research in the areas of cancer vaccination and immunomodulation:

**Cancer vaccination program:** Significant progress has been made in the application of current molecular and immunological techniques to discover novel tumor antigens over-expressed in patients with leukemias and breast cancer. For example, we have identified novel anti-WT1 regulatory T-cell clones (epitopes). These regulatory T-cell clones can be depleted using antibodies directed against their TCR v-beta. Consequently the immunogenicity of T-cells added back to patients after BMT/HSCT is enhanced and induces a strong GVL. On the other hand, patients with GVHD could be vaccinated with epitopes to enhance the frequency of anti-WT1 regulatory T-cell clones leading to a reduction of the severity of GVHD. More in vitro/in vivo investigations are required and clinical trials will be designed and implemented based on such epitopes in the near future. We are planning to use the HLA DR4-transgenic mice to investigate the inhibition effect of these T Regulatory T-cells on the treatment of human leukemia.

**Immunomodulation program:** The aim of this program is to design immunological tools that inhibit signals generated by over-expressed molecules on tumor cells. An example is to investigate the over-expression of B7-H1 in breast cancer patients and design specific antibodies to target this molecule. We have shown, for the first time, the expression of B7-H1 in 53% of breast cancer patients and demonstrated its expression as tumor specific. Moreover, the expression of B7-H1 was also present in tumor infiltrating lymphocytes (TIL). Interestingly, our findings indicate that B7-H1 correlates with important prognostic factors associated with high-risk patients. B7-H1 expression may represent a significant additional risk factor in breast cancer patients with advanced disease and suggests its involvement in the immune escape of tumors in breast cancer. We were the first group to provide direct evidence of the association between B7-H1 expression and proliferation. We are planning to continue studying the relationship of this molecule to other inhibitory factors such as T regulatory cells. In collaboration with Prof. Otto Majdic (Institute of Immunology, University of Wien, Austria), we have obtained an anti-B7-H1 monoclonal antibody which works on paraffin-embedded archived samples. This antibody will be used to analyze the expression of B7-H1 molecule in a large number of breast cancer

patients and correlated with a 5-year patient survival program to determine its usefulness as a diagnostic or prognostic factor in breast cancer patients.

The development of reliable and sensitive assays to monitor immune responses in cancer patients after treatments/vaccines is an important goal in tumor immunology. To this effect, we are introducing a sensitive and a reliable technique (ELISPOT) to measure the natural immune responses of leukemia patients in remission to 2 important tumor antigens (Proteinase 3 and WT1).

## PUBLICATIONS

### Peer Reviewed Articles

- H Ghebeh, E Barhoush, A Tulbah, N Elkum, T Al-Tweigeri, S Dermime. Foxp3<sup>+</sup> T<sub>regs</sub> and B7-H1<sup>+</sup>/PD-1<sup>+</sup> T lymphocytes co-infiltrate the tumor tissues of high-risk breast cancer patients: Implication for immunotherapy *BMC Cancer* 2008 Feb 23;8(1):57 [ahead of print].
- C Lehe, H Ghebeh, G Al Qudaihi, A Al-Sulaiman, K Al-Hussein, A Tbakhi, F Almohareb, N Chaudhri, H Alzahrani, M Aljurf, S Dermime. Human CD4<sup>+</sup> regulatory T-cells specifically recognize an immunodominant peptide derived from the leukemia-associated WT1 antigen: Implications for immunotherapy *Cancer Research* (in revision).
- N Elkum, S Dermime, D Ajarim, A Al-Zahrani, A Alsayed, A Tulbah, O Almalik, M Alshabanah, A Ezzat and T Al-Tweigeri. Age 40 and younger is an independent risk factor for relapse in operable breast cancer patients: The Saudi Arabia experience. *BMC Cancer*. 2007 Dec 5;7(1):222 [ahead of print].
- H Ghebeh and S Dermime. Characterization of human lung tumor-associated fibroblasts and their ability to modulate the activation of tumor-associated T-cells. Comments in: *Journal of Immunology* 2007; 179:732
- H Ghebeh, A Tulbah, S Mohammed, N Elkum, SM Bin Amer, T Al-Tweigeri, S Dermime. Expression of B7-H1 in breast cancer patients is strongly associated with high proliferative Ki-67-expressing tumor cells. *Int J Cancer*; 2007; 121:751-758.
- Al-Alwan MM, Du Q, Hou S, Nashed BF, Fan Y, Yang X, and Marshall AJ. Follicular dendritic cell secreted protein (FDC-SP) regulates germinal center responses. [*Journal of Immunology*. 2007 June 15; 178(12):7859-67].
- Marshall AJ, Zhang T and Al-Alwan MM. Regulation of B lymphocyte activation by the PH domain adaptor Bam32/DAPP1. [*Biochemical Society Transactions*. 2007 Apr; 35(2):181-2].
- Al-Alwan MM, Okkenhaug K, Vanhaesebroeck B, Hayflick JS and Marshall AJ. Requirement for the phosphatidylinositol 3-kinase p110 $\delta$  signaling in B cell antigen receptor-mediated antigen presentation. [*Journal of Immunology*. 2007 Feb 15; 178(4):2328-35].
- Cheung SMS, Kornelson JC, Al-Alwan MM and Marshall AJ. Regulation of phosphoinositide 3-kinase signaling by oxidants: Hydrogen 3 peroxide selectively enhances immunoreceptor-induced recruitment of 4 phosphatidylinositol (3,4) bisphosphate-binding PH domain proteins. [*Cellular Signalling*. 2007 May; 19(5):902-12].
- Nashed BF, Zhang T, Al-Alwan MM, Srinivasan G, Halayko AJ, Okkenhaug KT, Vanhaesebroeck B, Hayglass K and Marshall AJ. Role of the phosphoinositide 3-kinase p110 $\delta$  in generation of type 2 cytokine responses and allergic airway inflammation. [*European Journal of Immunology*. 2007 Feb; 37(2):416-24]

### Abstracts

- S Dermime, C Lehe, H Ghebeh, A Al-Sulaiman, G Al Qudaihi K Al-Hussein, F Almohareb, N Chaudhri, F Alsharif, H Al-Zahrani, A Tbakhi, M Aljurf . The leukemia-associated WT1 antigen is a new target for human CD4<sup>+</sup> regulatory T-cells: Implications for immunotherapy. KHCBI NCI Duke University MIDDLE EAST AND NORTH AFRICA (MENA) CANCER RESEARCH CONFERENCE, September 3-4, 2007, Grand Hyatt Hotel, Amman – Jordan.
- Cynthia Lehe, Hazem Ghebeh, Ghofran Al Qudaihi, Abdullah Al-Sulaiman, Khaled Al-Hussein, Abdelghani Tbakhi, Fahad Almohareb, Naeem Chaudhri, Hazza Alzahrani, Mahmoud Aljurf, Said Dermime. Characterization of novel anti-WT1 antigen specific human CD4<sup>+</sup>CD25<sup>+</sup>FOXP3<sup>+</sup> regulatory T-cell clones: Implications for leukemia immunotherapy. World Immune Regulation Meeting, Davos, Switzerland, April 11<sup>th</sup>-15<sup>th</sup> 2007.

Hazem Ghebeh<sup>1</sup>, Eman Barhoush<sup>1</sup>, Asma Tulbah<sup>2</sup>, Cynthia Lehe<sup>1</sup>, Taher Al-Tweigeri<sup>3</sup>, Said Dermime. Synergistic effect of Foxp3<sup>+</sup> T regulatory T-cells and T-cells expressing B7-H1 in the immune escape of breast cancer patients. World Immune Regulation Meeting, Davos, Switzerland, April 11<sup>th</sup>-15<sup>th</sup> 2007.

# **TRAINING AND EDUCATION**



The Research Centre

# TRAINING AND EDUCATION COMMITTEE

The Research Centre Training and Education Committee (RCTEC) was formed to provide and organize training and education activities in the Research Centre. It is designed to develop, promote, administer and implement education guidelines and procedures; and to organize in-house training in progressive fields of science and technology. Special courses and workshops are offered throughout the year.

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**Research Centre Training and Education Committee (RC-TEC)**

*Chairman*

**Refaat Al-Mazrou, MSc, MIPEM**

*Members*

- Ayodele Alaiya, PhD (BMR)
- Anas Al-Azami, DPhil (ADL)
- Abdalla Al-Haj, PhD (BMP)
- Ibrahim Al-Jammaz, PhD (CRD)
- Ahmed Al-Gahtani, PhD (BMR)
- Yasmin Al-Twajiri, PhD (BESC)
- Ali Al-Odaib, PhD (GD)
- Sahal Al-Hajjo, PhD (CMD)
- Huda Abdulaziz Al-Mosallam, Manager (TEO)

**Research Centre Training and Education Office (RC-TEO)**

*Director*

**Refaat Al-Mazrou, MSc, MIPEM**

*Manager*

Huda Abdulaziz Al-Mosallam

*Staff*

- Faten Al-Khateeb
- Abdulrahman Al Lahoo
- Gina Rodil
- Jamila Mae Fernandez
- Arwa Fayyad

## EXPERTISE

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The RCTEC facilitates external training and education for Saudi Arabians who wish to pursue MSc and PhD degrees and Postdoctoral Fellowship. Networks of partnerships with reputable scientific and educational local and international institutions have been established to ensure that the latest technology is acquired and career development is advanced.

## ACTIVITIES

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The Research Center Training and Education Committee and its office administer the following programs:

### Graduate Assistantship (GA)

The Research Centre offers eligible non-employee candidates the opportunity to pursue MSc or PhD in biomedical sciences in collaboration with scientific and educational institutions. Under this program the Research Center has received a scholarship funds from the King Khalid Foundation. The fund was directed towards higher education for Saudi Women. The fund began in 2003 and aims to provide Saudi women who are holding a Bachelor, Master and/or PhD degree/s in biomedical sciences with the opportunity to develop their scientific skill through various scholarship programs. Eligible candidates can pursue their research studies abroad or at the KFSH&RC in collaboration with recognized international universities and institutes, in the following disciplines:

- Graduate Study (MSc and PhD)
- Scientific Training
- Postdoctoral Fellowship

### In-House Training (I-HT)

The Research Centre provides training opportunities for eligible candidates from other institutions. These include:

- Undergraduate students who are seeking training related to their university degree
- Individuals who are seeking training to enhance their qualifications
- Saudi Arabian employees in public and private

sectors who want to develop an aptitude for research

- Recipients of Fellowship sponsored by international institution such as the Institute of Atomic Energy Research (IAEA) seeking on-the-job training
- Medical Fellows/Residents for training in research methodology
- High School students interested in a career in biomedical sciences will be given a short orientation.

### Postdoctoral Fellowship (PDF)

This is a program of study and research training at an institution abroad for employees of the Research Centre. The Fellowship, of maximum duration two years, should be relevant to the employees' work and the future directions of the Research Centre. The program is under the Hospital Scholarship guidelines.

### Hospital Scholarship (HS)

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 skill. The scholarship can be given either as Out-of-Kingdom Study Program (O-KSP) or In-Kingdom Study Program (I-KSP).

### In-House Graduate Research for Non-RC Employees (I-HGR)

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.

### Saudi Career Development Program (SCDP)

The Program is designed to chronologically identify the unique skills and special knowledge necessary to effectively perform the target job. The Program aims to develop the individual's scientific skill and knowledge based on his/her background to help meet the qualifications required for the target job after one year of training. The Research Centre offers career development to well-qualified Saudi graduates who wish to enhance their scientific and technical development.

**Volunteer (Volu)**

This program is for those qualified candidates who have hands-on experience in a specific field of science and interested to expand their skills through volunteering.

**Future Scientists (FS)**

The aims of this program are to assist talented young Saudi nationals in the acquisition of scientific skill, 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.

**Research Center Seminar (RCS)**

RCTEC represented by its office do organize a weekly seminar to be given by Research Center scientist. Invited seminars also take place from time to time in

the Research Center through the close collaboration between the Office and the concerned department.

**Workshop and Conferences (WS&Conf)**

The Research Centre Training and Education Office assists in organizing a number of annual workshops, conferences and special courses in specific field of science.

**Other Responsibilities**

RCTEC processes and ensures that all necessary guidelines are applied to the following leave categories:

- Business Leave (BL)
- Professional Leave (PL)
- Sabbatical Leave (SL)



# **MEDICAL AND CLINICAL OPERATIONS**



# DENTISTRY



The Department of

# DENTISTRY

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*Director*  
**Abdulhadi Abanmy, BDS, DMSc**

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## RESEARCH ACTIVITIES

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### The Section of Endodontics

#### 1. Outcome of Endodontic Treatment in Organ Transplant Patients. RAC #: 2071033.

**Investigators:** Dr Abdulrahman Al Dawood (PI), Dr Tariq Al Ali, and Dr Mats Eckerbom

#### Project description

To assess the outcome of Endodontic treatment in solid organ transplant patients

#### Background

The number of organ transplantation is growing world wide. Five years data collected at KFSH&RC demonstrated an increasing trend for organ transplant procedures. Prior to their operation, transplant candidates need a Dental Clearance. Afterwards, transplant recipients need a proper Dental Care/Treatment for the rest of their live. Dental treatment can either be Conservative or Radical. While radical approach is mainly through dental extraction, Endodontic Treatment is a symbol of the conservative approach; its main objective is to eliminate dental inflammation/infection and save the patient's natural teeth.

#### Materials and Method

A total of 674 patients who received solid organ transplants in the last five years at KFSH&RC are potential candidates for this study. Patient's medical/dental records will be reviewed; teeth that received endodontic treatment shall be identified as study subjects. Patients who fulfill the inclusion criteria shall be booked for a Clinical and Radiographic evaluation.

The Clinical Assessment Protocol CAP (an internationally accepted clinical evaluation protocol) will be performed by one of the examiner. The Periapical Index Scoring System PAI (an ordinal scale of five scores ranging from 1=healthy to 5 = severe apical periodontitis) will be the basis for analyzing the radiographs of the subject tooth/teeth to evaluate their periapical status. The radiographic evaluation shall be performed by two specialist endodontist. Based on a combination of the CAP and the PAI result, the outcome of the endodontic treatment shall be categorized in one of the following: Success, Questionable or Failure.

### Rational/Significance

The lack of definitive dental treatment protocols for organ transplant patients has been well acknowledged. Up to date, there is no sound evidence supporting or contradicting the provision of Endodontic Treatment for organ transplant patients, although, there are various factors which may impact the outcome of that treatment in those patients ( either due to their medical condition and/or due to their drug therapy). We are optimistic that this study may add up to our knowledge for better understanding of the outcome of endodontic treatment in this group of patients. Consequently, it will enable dental care professionals to decide on the most appropriate dental treatment protocol for this important category of tertiary care patients.

### The Section of Pediatric Dentistry

#### 1. Prevalence of Cleft Lip and Palate in Hospital based Population KFSH&RC. RAC #: 991030.

**Investigators:** Dr Aziza Al-Johar, Dr Kandasamy Ravichandran and Ms Shazia Subhani

#### Project description

#### Objective

To report the patterns of cleft lip and/or cleft palate in Saudi Arabia from data collected at a tertiary care hospital.

#### Design and setting

King Faisal Specialist Hospital & Research Centre, Riyadh

#### Patients

All the cleft lip and/or cleft palate patients registered in the Cleft Lip/Palate and Craniofacial Anomalies Registry from June 1999 to December 2005.

#### Results

Retrospectively, 807 cases of cleft lip and/or palate were registered.

There were 451 boys and 356 girls. Cleft lip and palate was more common (387) than isolated cleft palate (294) and isolated cleft lip (122). Boys predominated in cleft lip and palate and cleft lip, whereas girls predominated in isolated cleft palate, with boy to girl ratios of 1.6: 1, 1.2:1 and 0.9 :1 for cleft lip and/or palate, isolated cleft lip, and isolated cleft palate, respectively. The Riyadh region had more cases (32.0%) than the Asir (15.6%)

regions. Parents of 439 individuals had consanguineous marriages. A positive family history of cleft was seen in 224 cases. Of the 238 cases with associated anomalies, 91 had congenital heart disease. Of the children with isolated cleft palate, 40.5% had associated anomalies, whereas only 23.0% of the children with isolated cleft lip or isolated cleft palate had associated malformations.

### Conclusion

The pattern of cleft observed in this study does not differ significantly from those reported in the literature for Arab populations.

### Publication

Al-Johar A, Ravichandran K, Subhani S. "Pattern of Cleft Lip and Palate in Hospital based Population in Saudi Arabia: Retrospective Study". Published in the *Cleft Palate-Craniofacial Journal*, March 2008. cpcj- 45-05-11.3d

### 2. Pediatric Hemophilia & Von Willebrand Registry. RAC #: 2041040.

**Investigators:** Dr Owaida, Dr Al Musa, Dr. Z Alkhalayal, Dr Al Saleh

### Project description

Hemophilia and Von Willebrand diseases are a group of congenital bleeding disorders that may complicate dental treatment. Optimal oral health and prevention is very important in this group.

The aim of the registry is to have a baseline data on the oral status of patients with hemophilia and Willebrand's disease.

### The Section of Prosthodontics

#### 1. Gene Expression & Immuno-histological findings in patients with Papillon-Lefevre Syndrome. RAC #: 2070022.

**Clinical Investigators:** Adeeb Al Omrani BDS, DMSc(PI), Saleh Al-Muhsen, MD, Hamad Al Zaidan, MD, Mohammed Al Owain, MD, Richard Hakansson, DDS, PhD, Christer Ullbro, DDS, PhD

**Research Investigators:** Namik Kaya, PhD (Co-PI), Dilek Colak, PhD, Said Dermime, PhD, Hazem Ghebeh, PhD

### Project description

#### Abstract

Papillon-Lefevre syndrome is an autosomal recessive disorder characterized by hyperkeratosis of palms 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.

#### 2. Rare Dental Disorder Registry. RAC #: 2071082.

**Investigators:** Dr Adeeb Al Omrani (PI), Dr Hans Hansson, Dr Richard Hakansson, Dr Khalid Al Zoman, Ms Shazia Naz Subhani

### Project description

#### Abstract

Congenital Oral Anomalies are a broad category of health conditions that are present at birth and are a deviation from normal anatomic growth, development, or function. There is an urgent need to increase knowledge about oral rehabilitation for people with oral/dental disabilities and new methods for treatment must be developed and evaluated. This will lead to better care and will have great influence on the quality of life for people with oral disabilities.

The aim of this registry is with a multi disciplinary team approach enhancing the opportunities for individuals with rare oral and facial disorders to get adequate information, diagnosis and treatment at King Faisal Specialist Hospital & Research Center, from all over the country.



# **EMERGENCY MEDICINE**



The Department of

## EMERGENCY MEDICINE

The research activities are supported by the Research Committee which reviews all departmental research and provides support. The committee has focused on developing and encouraging basic epidemiologic and descriptive research within the department. Another focus is research on administrative and quality improvement topics related to emergency department operations. The future plans will include a larger number of research projects focusing on prospective and interventional studies.

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*Chairman*  
Hisham Al-Omran, MD

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## ONGOING RESEARCH PROJECTS

### 1. Characteristics Of Pediatric Emergency Patients Presenting To A Tertiary Care Hospital, In Saudi Arabia. H.A.Kamal, G.M Qassim, H.A.Omran.

#### Objective

To describe the characteristics of pediatric emergency patients presenting to a tertiary care hospital, in Saudi Arabia.

#### Design

Prospective descriptive study.

#### Setting

Pediatric Emergency Department at King Faisal Specialist Hospital and Research Center in Riyadh, Saudi Arabia.

#### Patients/Participants

A total of approximately 2000 patients were consecutively identified over a nine-month period. Their ages range from 0 – 14 years old. Patients were excluded if they were direct admissions, referred for blood products or electrolytes replacement or solely for subspecialty service. In addition, patients who did not have a medical record in the Hospital Health System were excluded. Patients with more than one Emergency Department visit in the study period will be considered as an additional visit.

#### Intervention

None.

#### Measurements/main results

A Total of 1000 patients out of 2000 were seen and approached at the Pediatric Emergency Department during a four months period from (1<sup>st</sup> May 07- 31<sup>st</sup> Aug 07), their mean age 5.1 years (Min 0.01, Max14), male patients (53.66%) compared to female patients (46.12%). The data showed approximately 25% of the ED visits were categorized as CTAS levels 1, 2 or 3 while the remainders were level 4 and 5. Their waiting time from arrival to triage (Mean 5.6min, Min0.0min, Max107min,) from triage until seen by physician (Mean 56.8min, Min0.00 min, Max 385.0min) from seen by physician to disposition (Mean 56.8min, Min 0.00min, Max385.0min) and from arrival to disposition (Mean118.9 Min0.00 min, Max1265.0). The most common reasons for the Emergency Department visit were for: fever 33%, vomiting 18.76%, diarrhea 16.2%, others 15.6%, cough 14.47%, abdominal pain 6.92%,

runny nose 5.82%, shortness of breath 5.3%, sore throat 4.92%, minor injury 4.5%, head ache 2.9%, urinary symptoms 0.7% seizure 0.56% and decreased level of consciousness 0.1%. Most patients have an underlying disease and about 19.9% were healthy patients, the rest 15.6% other disorders: 8.83% cardiac, 8.55% seizure disorders, 8.1% gastroenterological disease, 6.66% neurological disease, 6.15% respiratory, 4.9% immune deficient/post transplants, 4.87% oncology patients, 4.38% metabolic disorder, 3.21% renal disease, 1.2% hematology, 0.87% endocrinology and 0.33% rheumatologic disease.

#### Conclusion

The characteristics of pediatric patients presenting to King Faisal Specialist Hospital & Research Center have no specific difference from other tertiary hospital in North America. So the Emergency Department collected data would serve as a baseline for further research into disease or patient specific characteristics and as a tool to compare pediatric emergency utilization patterns with health care institutions in North America, the Middle East and the developing world.

Presented at the Annual European Society of Emergency Medicine Conference, Italy 2007.

### 2. Validity Of The Canadian Triage An Acuity Scale At A Tertiary Care Center In Saudi Arabia. G Bakhidar, A AIdarrab.

#### Background

The Canadian Triage and Acuity Scale (CTAS) is a 5-level triage tool, with 1 being the most acute. It has been shown to be a reliable and valid triage tool in Canada. In 2002, CTAS was first instituted at our tertiary care center in Saudi Arabia. However, it has never been evaluated in our population.

#### Objective

We seek to evaluate the validity of CTAS in predicting hospital admission at our tertiary care center in Saudi Arabia.

#### Methods

Our Emergency Department (ED) sees 45000 visits per year with an overall admission rate of 9%. A retrospective study of all patients presenting to our ED from September 1<sup>st</sup> until September 30<sup>th</sup> 2007 was performed. The CTAS category and ultimate disposition for each patient was recorded. For this study ED death and hospital transfer were considered as admissions.

**Results**

During the study period 4108 patients visited the ED and 3636 were included in the final data analysis. Four hundred seventy two patients were excluded due to missing or incomplete data. The total number in each triage category was: 18 (CTAS1), 150 (CTAS2), 896 (CTAS3), 2098 (CTAS4), 474 (CTAS5). Hospital admission rates were: 67% (CTAS 1), 47% (CTAS2), 18% (CTAS3), 3% (CTAS4), 1% (CTAS5).

**Conclusion**

At our tertiary care center in Saudi Arabia, CTAS appears to be a valid triage tool that predicts patient disposition from the ED.

Presented at the Annual Residents Research Meeting at King Faisal Specialist Hospital 2007.

### 3. Accuracy Of Family Dosing Of Acetaminophen For Their Children With Fever In Saudi Arabia. N AlRowaily, M Alomar.

**Goal**

To assess the adequacy of acetaminophen dosing by family members for their children with fever in Saudi Arabia and to discover the primary source of information for acetaminophen dosing for their children.

**Hypothesis**

Do the families in Saudi Arabia give their children with fever the correct dose of acetaminophen?

**Methods**

The study will be conducted in the setting of the emergency department KFSH&RC one of the biggest tertiary centers in Riyadh Saudi Arabia over a period of three months. In this study our target number of patients (200-300 patients) will be reviewed by cross-sectional observational study of children who received acetaminophen by their families for fever in the prior one day before coming to emergency room. The questionnaire will be completed by treating physicians.

Families will be consented verbally before answering the questionnaire as agreed by the research committee in the emergency department KFSH&RC. After completion of the questionnaire, it will be collected in a special box in the ER room.

**Inclusion criteria**

We included children between 0-13 years of age who received a known quantity of acetaminophen for suspected or confirmed fever within the last 24 hours before the ER visit.

**Exclusion criteria**

Children who received medication other than acetaminophen for fever. Children who received an unknown dose of acetaminophen. Children who received acetaminophen for reasons other than fever. Children who are not accompanied by their families. Based on previous studies recommendations, we considered the standard dose of acetaminophen 10-15mg/kg per dose, not mooses per day.

**Statistical Considerations**

Data collected will be analyzed by suitable software.

### 4. Chest Pain In A 12-Year-Old Boy When Is It A Harbinger Of Poor Outcome?

**Investigators:** F AlGhamdi, H Alomran.

Chest pain is a common and usually benign presentation in children who present to emergency departments or primary care providers. Unlike adults, where chest pain is commonly due to cardiac causes, in children the cause is more likely secondary to non-cardiac causes. Here we present a case of a child known to have Hyperesophilic Syndrome (HES) who presented to the emergency department with a sudden onset of chest pain and developed acute myocardial infarction (AMI) and died in the emergency department. We discuss the approach to the child with chest pain and review acute myocardial infarction in children.



# **FAMILY MEDICINE AND POLYCLINICS**



The Department of

**FAMILY MEDICINE &  
POLYCLINICS**

*Chairman*  
**Abdulaziz Al Nasser**

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## RAC-APPROVED RESEARCH ACTIVITY

### 1. The Outcome Of Hemopoietic Stem Cell Transplantation (HSCT) In Severe Combined Immunodeficiency Diseases (SCID): KFSH&RC Experience Compared To International Data. RAC205052.

**Investigators:** Al Muhsen S, Ayas M, Al Khamees N, Al Booq A, Al Ghonaium A, Shaheen H, Al Mousa H, Al Dhekri H, Arnaout R, Al Jefri A, Al Seraihy A, Hersi A, Al Rayes H, El Solh H

#### Overview

Transplantation of hematopoietic stem cells provide cure for severe combined immune deficiency patients. Data on long-term outcome of this treatment in our area is limited. Therefore, our objective was to determine the impact of stem cell transplantation on long-term outcome in patients with severe combined immune deficiency syndrome.

There were 108 transplants in 100 SCID patients that have been performed between Jan 1993 to Dec 2006. 54% were T-B- SCID, 13% were T-B+ SCID, 13% were adenosine deaminase deficiency (ADA) deficiency, 9% were Omenn syndrome, 6% were CD8 Lymphopenia, and 5% were unclassified with severe T cell dysfunction. The overall survival with sustained engraftment at the time of analysis was 83%. Patients with T-B+ (91% survival) had better prognosis than T-B-SCID (83% survival). Transplant from HLA- Genoidentical matched donor was associated with the best outcome (89% survival). On the other hand ADA deficiency had the worst outcome (71%). Patients received reduced intensity conditioning before stem cell transplantation had the most favorable outcome (95% survival), while non-conditioned patients had lower survival rate (83%). The worst prognosis as expected for patients received myelo-ablation (70% survival). However, among those who survived; patients received myelo-ablative chemotherapy had more stable engraftment and better immune reconstitution. Immune reconstitution and chimeric studies will be shown.

Hematopoietic stem cell transplantation provides long-term cure and survival for SCID. Whenever available, genoidentical HLA matched donor is the best source for stem cells. Myelo-ablation is not indicated for matched related HSCT in SCID and can cause unnecessary morbidity and mortality. Reduced intensity conditioning might be an option especially if it correlated with stable

engraftment and long-term immune reconstitution. Further prospective long-term studies are required.

### 2. Underlying Molecular Genetic Defects Of Severe Combined Immunodeficiencies (SCID) In Saudi Arabia, RAC 2060120.

**Investigators:** Hamoud Al-Mousa, Osama Alsmadi, Abdulaziz Al-Ghonaium, Hasan Al-Dhekri, Hassan Al-Rayes, Saleh Al-Muhsen, Rand Arnaout, Abdelghani Tbakhi, Dorota Monies, Salma Wakil

#### Overview

Severe combined immunodeficiencies (SCID) represent the most severe form of primary immunodeficiencies. At least ten different forms of human SCID have now been recognized and can be grouped according to inheritance, phenotype, and for some of them, identification of the mutated genes. All SCID phenotypes are seen in the Kingdom, but up to date the underlying molecular genetic defects of those patients are not identified. The specific aim of this study is to identify the underlying molecular genetic defects of SCID in Saudi Arabia. All retrospective and prospective patients with the diagnosis of SCID under follow-up at KFSH&RC in primary immunodeficiency clinics or the post bone marrow transplantation clinic will be identified. Based on SCID phenotype, individuals will be screened for mutations in most likely genes that fit the clinical and laboratory presentation of SCID. Up to date, more than 40 families with SCID disease had been studied; mutations in RAG1, RAG2, Artemis, Jak3 and ADA genes have been identified; some were novel mutations. Families of patient's negative for mutations of the known SCID genes who demonstrate a strong family history will be utilized for subsequent linkage analysis depending upon statistical power of pedigrees and accessibility to family members that may identify novel genetic defects. It is expected that data resulting from this study will benefit future counseling and newborn screening programs.

### 3. Allogenic HLA-Identical Bone Marrow Transplantation In Major Histocompatibility Complex Class II (MHC II) Deficiency: A Single Center Study, RAC 2051049

**Investigators:** Hamoud Al-Mousa, MD, Zamil Al-Shammari, MD, Samira Rifai, MD, Abdulaziz Al-Ghonaium, MD, Hasan Al-Dhekri, MD, Hassan Al-Rayes, MD, Saleh Al-Muhsen, MD, Rand Arnaout, MD, Abdelghani Tbakhi, MD, Samer Markiz, MD, Ashraf Radwan, MD, Othman Mosleh, MD, Amal Al Seraihy, MD

## Overview

Major Histocompatibility Complex Class II (MHC II) deficiency is a rare combined immunodeficiency disease characterized by profoundly deficient HLA class II expression, inconsistent and incomplete expression of HLA class II molecules, and lack of cellular and humoral immune responses to foreign antigens. Clinical manifestations include extreme susceptibility to viral, bacterial, fungal and protozoal infections, primarily of the respiratory and gastrointestinal tract. Severe malabsorption with failure to thrive ensues, often leading to death in early childhood.

MHC II deficiency has an autosomal recessive mode of inheritance. The majority of patients are of North African and Middle East origin although patients from other ethnic backgrounds had been reported. The diagnosis of MHC II deficiency in patients referred to immunodeficiency clinics at KFSH&RC with history of recurrent infections is not unusual. Disease has been noticed in certain tribes. The disease incidence at Saudi Arabia has not been studied yet.

The disease is due to defects in several distinct trans-acting regulatory factors required for expression of MHC II genes. Three of these genes, MHC2TA (OMIM number = 600005), RFX5 (OMIM number = 601863), and RFXAP (OMIM number = 601861), have been isolated and shown to be mutated in MHC II deficiency patients.

Allogeneic Bone Marrow Transplantation (BMT) is considered the only available curative treatment for MHC II deficiency. BMT can cure the disease, provided it is performed before complications leading to severe organ failure develop (Klein et al, 1995). The relatively low overall success rate of bone marrow transplantation when compared to some of the other forms of immunodeficiency (i.e., only a 54% survival rate following HLA-identical transplantation) possibly reflects the considerable heterogeneity in clinical presentation of these disorders and in the age at transplantation.

Two interesting observations have been made in long-term survivors of successful transplants (Klein et al, 1995): 1) persistence of a relative CD4 T-cell lymphopenia – possibly due to a lack of HLA class II molecules on thymic epithelial cells – even though the donor derived CD4+ T cells are functional, and 2) defective expression of HLA class II molecules on non-hematopoietic cells appear to have no detrimental consequences.

## 4. Allogeneic Bone Marrow Transplant In Leukocyte Adhesion Defect 1: A Single Center Study, RAC 2051053.

**Investigators:** Hassan Dhekri, MD, Abdulaziz Al-Ghoniaim, MD, Abdullah Al Jefri, MD, Hamoud Al Mousa, MD, Rand Arnaout, MD, Saleh Al Muhsen, MD, Abdelghani, Tbakhi, Mouhab Ayas, MD, Mohammed Mahr, MD, Lyla Osman, MD, Hasan Shahin, MD, Hassan Rayes, MD.

### Overview

Leukocyte Adhesion Deficiency Type 1 (LAD-1) is rare autosomal recessive immunodeficiency disorder. The severe phenotype is fatal unless bone marrow transplantation (BMT) is performed. We describe here the outcome of LAD patients underwent BMT in KFSH&RC.

Six patients with LAD-1 underwent bone marrow transplantation (BMT) from matched sibling. Median age at diagnosis was 6.75 months and at BMT was 10.1 months. Five were full match genodisordered. Conditioning included cyclophosphamide and busulphan. Two received extra Alemtumab (CAMPATH) and Etoposide VP16+ATG respectively graft versus host disease (GVHD) prophylaxis were cyclosporine A (CSA) in 6/6 and methotrexate added to CSA in 3/6. Five patients engrafted, mixed chimerism in four patients and full in one patient. CD18 expression as low as is protective. One patient had acute GVHD; none had chronic GVHD. We concluded that full-match genodisordered BMT for LAD has an excellent outcome with a minimal GVHD complications.

## 5. The outcome of hematopoietic stem cell transplant for Wiskott-Aldrich Syndrome patients: A single center study, RAC 2051051.

**Investigators:** Rand K. Arnaout, MD, Abdulaziz Al Ghoniaim, MD, Hassan Al Rayes, MD, Saleh Al Muhsen, MD, Hasan Al Dhekri, MD, Hamoud Al Mousa, MD, Abdulghani Tbakhi, MD, Tareq Oweida, MD, Amal Al Seraihi, MD, Mohab Ayas, MD, Samira Al Rifai, MD, Hassan El Solh, MD

### Overview

Wiskott-Aldrich Syndrome (WAS) is a rare mostly X-linked form of immunodeficiency characterized by thrombocytopenia, eczema, recurrent infections, autoimmunity, and an increased incidence of

malignancy. Clinical severity is highly variable so is therapeutic modalities. Currently stem cell transplant with all its modalities is the only curative treatment. We retrospectively analyzed the results of our WAS patients at KFSH&RC from both Hematology/Oncology database and Immunology database between 1993-2006.

**Project description, progress, major findings**

We had records of 22 Wiskott-Aldrich patients, seven (7) of which did not go for transplant for different reasons. Fifteen (15) patients underwent stem cell transplant which is equivalent to 68%. Out of these 15 patients, only 1 patient had match unrelated donor (MUD) transplant, 4 patients got Cord blood transplant, equivalent to (26.6%) with 50% survival and 10 patients

got Allogenic BMT from related HLA-matched donor with 100% survival.

Our overall survival in our cohort of patients is 80%. All are doing well. We have a 20% mortality rate; most of the mortality is secondary to intracranial bleeding and or infection.

Our results are comparable to results from United States, Japan and Europe.

The project was finalized, submitted to the RAC and accepted the final report. It was presented in a poster in the International Stem Cell Congress at KFSH&RC in November 2007, and an abstract was submitted to BMT Journal to be published in the proceedings.

# **KING FAISAL CANCER CENTRE**



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## KING FAISAL CANCER CENTRE

The King Faisal Cancer Centre (KFCC) is a newly established structure for cancer care of adult patients with a mission of providing excellent cancer treatment, education and research by means of integrated team work and the vision to become the best international centre for cancer research, prevention, and treatment. Accredited by the World Health Organization (WHO) as a Collaborating Centre for Cancer Prevention and Control, KFCC patients are assessed in multidisciplinary clinics and treated in accordance with disease specific internationally accepted management guidelines. The Research Unit provides support for research projects and serves as a hospital base for cancer and bone marrow transplantation registries. KFCC continues to be actively involved in institutional, national, and international research protocols with priority given to those addressing national oncology problems. KFCC houses the National Cancer Registry and the Gulf Council Countries (GCC) Cancer Registry which defines population-based incidence of cancer in the Kingdom. The goal of KFCC is to establish an internationally renowned Cancer Institute to meet the ever growing needs of patients with cancer and hematological disorders.

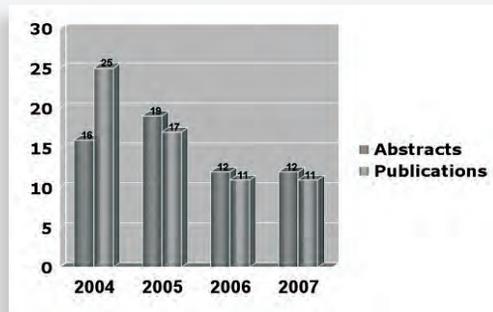
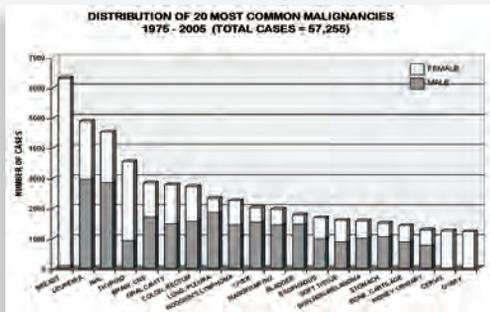
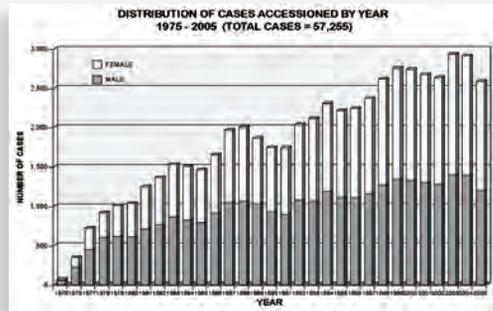
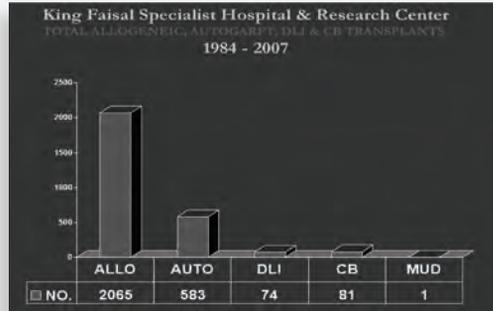
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*Director*  
Dahish Ajarim, MD

### *Members*

Fahad Al-Mohareb  
Shouki Bazarbashi, MD  
Mohammad Al-Shabanah, MD  
Tarek Amin, MD  
Naeem Chaudhri, MD

- Received membership of the Radiation Therapy Oncology Group (RTOG), making KFCC the only RTOG center in the Eastern Mediterranean region.
- Membership of South West Oncology Group (SWOG) and Cancer and Leukemia Group B (CALGB) are in progress.
- Installation of updated CIBMTR software (STEMSoft) for effective Bone Marrow Transplant data management. Organized CIBMTR/NMDP teleconferences to learn about new advances and paradigms in the BMT registry.
- Installation of newly customized Tumor Registry Software (CNEXT).
- Published 2005 Tumor Registry Annual Report and 2006 report is in progress.
- Established an exchange program with major cancer center in North America for KFCC Tumor Registrars to learn benchmark program for 1 – 2 weeks and apply best practices to our program.
- Enhanced education & training: Two Clinical Research Coordinators attended the two weeks Clinical Research Professional Course organized by the ORA.
- Activated NCI Protocol Registration System (PRS) to register all the KFCC clinical trials.
- Promoted translational research program with the scientists from the Research Center for translating basic research findings into clinical research questions. The goal is to bring the promising developments found in the laboratory into clinical research.
- New KFCC website was created with myriad of medical, scientific and patient education information and is being continuously updated with current guidelines.
- Created a bridge between community physicians, researchers and medical students to provide cancer facts & figures, to enhance cancer education and encourage primary prevention.
- Poster presented for Quality Day 2007 to represent KFCC: "Communication is the optimizer in quality health care in KFCC"
- Organized "Biostatistics Course-All you need to know": 4 CME credit course on 25 November 2007: Very successful and received high accolade.
- Created digital database and forms for the Gulf Breast Study (GORG-001).
- Initiated several new studies including Zevalin for Diffuse Large B Cell Lymphoma and A randomized phase II study comparing ALIMTA (Pemetrexed) plus best supportive care with best supportive care as maintenance, following first line treatment with pemetrexed-cisplatin, in patients with advanced NSCLC (Lilly) and Lymphoma & Hepatitis B Reactivation.
- Organized very successful International Symposium on Bone Marrow and Stem Cell Transplantation from 13-15 November, 2007, which was attended by world renowned speakers from the Gulf region, Europe and North America.
- Second Academic and Research Day planned for 7<sup>th</sup> May 2008 at KFSH&RC for the Oncologists from Cancer Centers in Riyadh.



## RESEARCH PROJECTS

### Database

1. **Project title: Prospective Data Collection Of Newly Diagnosed Breast Cancer Cases. RAC # 2051 029.**

**Investigators:** Ajarim D, Twegieri T.

**Project description**  
Breast Database.

**Progress**  
Active.

### Protocol

1. **Project title: RTOG 0417 – 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**

**Investigators:** Al-Rajhi, N.

**Project description**  
Protocol.

**Progress**  
For approval.

2. **Project title: RTOG 0525 – Phase III Trial Comparing Conventional Adjuvant Temozolomide with Dose Intensive Temozolomide in Patients with Newly Diagnosed Glioblastoma. RAC # 2081-018**

**Investigators:** Al-Rajhi, N.

**Project description**  
Protocol.

**Progress**  
For approval.

3. **Project title: RTOG 0627 – Phase II Trial of Dasatinib in Patients with Recurrent Glioblastoma Multiforme. RAC # 2081-013**

**Investigators:** Al-Rajhi, N.

**Project description**  
Protocol.

**Progress**  
For approval.

4. **Project title: Open-Label Study Of Bevacizumab (Avastin)® Plus Taxane Monotherapy Or In Combination For The First-Line Treatment Of Patients With Locally Recurrent Or Metastatic Breast Cancer. RAC # 2071 026**

**Investigators:** Al-Sayed A.

**Project description**  
Protocol.

**Progress**  
Active.

5. **Project title: A SU011248 expanded Access Protocol For Systematic Therapy Of Patients With Metastatic Renal Cell Carcinoma Who Are Ineligible For Participation In Other SU011248 protocols But May Derive Benefit From Treatment With SU011248. RAC # 2061 043**

**Investigators:** Bazarbashi S.

**Project description**  
Protocol

**Progress**  
Active

6. **Project title: Phase II trial of Neoadjuvant [FEC100]/ Cisplatin-Docetaxel ± Trastuzumab In Women With Over Expressed Or Amplified Her2/Neu With Locally Advanced Breast Cancer. RAC # 2061 048**

**Investigators:** Twegieri T, Ajarim D.

**Project description**  
Protocol.

**Progress**  
Active.

7. **Project title: An open-label, multicenter, expanded access study of oral AMN 107 in adult patients with Imatinib (Glivec®/Gleevec® - resistant or intolerant**

chronic myeloid leukemia in blast crisis, accelerated phase or chronic phase. RAC # 2071 008

**Investigators:** Chaudhri N,

**Project description**  
Protocol

**Progress**  
Active

## RESEARCH STUDY

G. Alsbeih, K. Balaraj, M. El-Haddad, M. El-Sebaie, J. Al-Mokhlef Cervix Carcinoma, HPV Infection, Genetic Predisposition and Biomarkers of Response to Chemoradiation Therapy (RAC # 2060 029)

**Registry**

- Project title: Protocol Amendment No. 1 – Adjuvant Colon Cancer with ELOXatin@/5 FU Based Regimen: ACCELOX**

**Investigators:** A. Al-Jubran

**Project description**  
Registry.

**Progress**  
Active.

- Project title: Int'l. Bone Marrow Registry (Autologous Transplant)**

**Investigators:** Section of Adult Hematology/BMT

**Project description**  
Registry (BMT- Autologous Transplant).

**Progress**  
Continuous accrual, NP CRF 2500 to 3000 variables. FU CRF-1000 variables ; active; accrue approx. 30 per year and follow-up.

- Project title: European Bone Marrow Registry**

**Investigators:** Adult and Pediatric Hematology

**Project description**  
Registry (BMT).

**Progress**  
Active; continuous accrual.

- Project title: Post Operative Adjuvant Chemotherapy Followed By Adjuvant Tamoxifen vs Nil for Patients With Operable Breast Cancer – EORTC. (RAC#93-107)**

**Investigators:** A Ezzat, S Bazarbashi, M Raja

**Project description**  
Prospective Research Protocol: Breast Cancer

**Progress**  
Follow-up only.

- Project title: Using Support Vector Machines For Prognosis And Survival Prediction In Breast Cancer. (RAC# 2040-006).**

**Investigators:** T Twegieri, et al.

**Project description**  
Prospective Research Protocol: Breast Cancer

**Progress**  
Complete.

- Project title: Open Label, Randomized, Multicenter Study To Evaluate The Use Of Zoledronic Acid In The Prevention Of Cancer Treatment Related Bone Loss In Postmenopausal Women With ER+ and/or Pgr+ breast Cancer Receiving Letrozole As Adjuvant Therapy. (RAC #2031-089)**

**Investigators:** D Ajarim, T Twegieri

**Project description**  
Prospective Research Protocol: Breast Cancer

**Progress**  
Inactive.

- Project title: Phase II Study Of Neoadjuvant Chemotherapy With Doxorubicin Followed By Docetaxel-Cisplatin In Locally Advanced Breast Cancer. (RAC# 2011-022)**

**Investigators:** A Ezzat, et al.

**Project description**

Prospective Research Protocol: Breast Cancer.

**Progress**

Closed for accrual; for FU and TX completion.

- 8. Project title: Use of FDG PET As Predictor Of Residual Disease And Subsequent Relapse In Patients With NHL And HD Undergoing HDC And ASCT. (RAC# 2041-051)**

**Investigators:** S Akhtar, Sugarim Kadhi, A Ezzat, S Bazarbashi, I Maghfoor, M Rahal, A El-Weshi, M Abdelsalam, et al.

**Project description**

Prospective Research Protocol- Lymphoma.

**Progress**

Active; rapid accrual.

- 9. Project title: Cytogenetic Analysis Of Bone Marrow Specimen Prior To High Dose Chemotherapy And Autologous Stem Cell Transplantation ( In Patients With Non- Hodgkin's Lymphoma Or Hodgkin's Disease. (RAC# 2041015)**

**Investigators:** S Akhtar, I Iqbal, A Ezzat, S Bazarbashi, D Ajarim, I Maghfoor, A El-Weshi, M Raha.

**Project description**

Prospective Research Protocol-Lymphoma.

**Progress**

Active.

- 10. Project title: Randomized Phase II Trial On Primary Chemotherapy With High-Dose Methotrexate, Alone Or Associated With High Dose Cytarabine, Followed By Response And Age Tailored Radiotherapy For Immunocompetent Patients With Newly Diagnosed Primary Nervous System Lymphoma**

**Investigators:** A Abdelsalam, et al.

**Project description**

International study; prospective research protocol- Lymphoma.

**Progress**

Pending RAC approval.

- 11. Project title: Loss To Follow-Up In Lymphoma Patients**

**Investigators:** S Brown, et al.

**Project description**

Prospective Research Protocol-Lymphoma.

**Progress**

Closed; 2<sup>nd</sup> paper publication.

- 12. Project title: Phase II: Adjuvant And Neoadjuvant Chemotherapy In Operable Epidermoid Esophageal Cancer. (RAC# 981-021)**

**Investigators:** Bazarbashi, T Amin, S Bakheet, A Ezzat, El Fadda, C Pai. D Ajarim, M Raja, M Rahal, M Memon, Raningwala, M El Foudeh, J Powe.

**Project description**

Prospective Research Protocol- Esophageal cancer.

**Progress**

Follow-up; closed for accrual.

- 13. Project title: Randomized Phase III Trial Of Surgery Alone Or Surgery Plus Preoperative Gemcitabine-Cisplatin In Clinical Early Stages Of Non-Small Cell Lung Cancer. (RAC# 2031-059)**

**Investigators:** K Rehman, et al.

**Project description**

Prospective Research Protocol-Lung Cancer.

**Progress**

Follow-up only.

- 14. Project title: Phase III: Assess Conventional RT With Conventional Plus Accelerated Boost RT In The Treatment Of Nasopharyngeal Carcinoma. (RAC# 0971-004)**

**Investigators:** A Al-Amro, N Al-Rajhi

**Project description**

Prospective Research Protocol- Nasopharyngeal Cancer.

**Progress**

Survival follow-up only.

**15. Project title: Randomized Multicenter Study Of 5 vs. 6 weekly Fraction Of RT In The Treatment Of Squamous Cell Carcinoma(SCC) Of The Head And Neck. (RAC #0981-019)**

**Investigators:** A Al-Amro, N Al-Rajhi.

**Project description**

Prospective Research Protocol- Head and Neck.

**Progress**

Follow-up only.

**16. Project title: Organ Preservation: Weekly Carboplatin And Taxol With Concurrent RT for Locally Advanced Laryngeal And Hypopharyngeal Carcinoma. (RAC#0971-024)**

**Investigators:** A Al-Amro, M Memon.

**Project description**

Prospective Research Protocol- Laryngeal and Hypopharyngeal Cancer.

**Progress**

Active; very slow accrual.

**17. Project title: Phase II Trial Of Concurrent Administration Of Intravesical BCG And Interferon In The Treatment And Prevention Of Recurrence Of Superficial Transitional Carcinoma Of The Urinary Bladder. (RAC# 2011-073)**

**Investigators:** S Bazarbashi, et al.

**Project description**

Prospective Research Protocol- Urinary Cancer.

**Progress**

Active; slow accrual.

**18. Project title: Multi-national, Randomized, Phase III, GCG Intergroup Study Comparing Pegylated Liposomal Doxorubicin (CAELYX) And Carboplatin vs. Paclitaxel and Carboplatin In Patients With Epithelial Ovarian Cancer In Late Relapse. (RAC #2051-062)**

**Investigators:** K Rehman, et al

**Project description**

Prospective Research Protocol -Ovarian Cancer

**Progress**

New International Study

**19. Project title: Phase III Study of Cisplatin And RTX vs. RTX alone in squamous cell carcinoma of cervix**

**Investigators:** K Rehman, et al.

**Project description**

Prospective Research Protocol- Cervical Cancer.

**Progress**

Follow-up only.

**20. Project title: Randomized Trial Of Chemotherapy With Or Without Granulocyte Stimulating Factor In Operable Osteosarcoma. (RAC #931-009)**

**Investigators:** M Memon, S Bazarbashi, A Ezzat, et al

**Project description**

Prospective Research Protocol- Sarcoma

**Progress**

Follow-up only.

**21. Project title: Randomized study for the treatment of Ewing's Sarcoma of the bone (EORTC). (RAC #931-025)**

**Investigators:** A Ezzat, M Memon, S Bazarbashi, Al Sedairy, Kadhi, Moreau, et al.

**Project description**

Prospective Research Protocol- Sarcoma.

**Progress**

Follow-up only.

**22. Project title: Phase II Pilot Study Of Vincristine, Adriamycin, Actinomycin D, Ifosfamide combination Chemotherapy In Ewing's Sarcoma (RAC# 2031-065)**

**Investigators:** M Memon, Raja, et al

**Project description**

Prospective Research Protocol- Sarcoma.

**Progress**

Active; slow accrual.

**23. Project title: Randomized Study For The Treatment Of Ewing's Sarcoma Of The Bone (EORTC). (RAC#931-025)**

**Investigators:** A Ezzat, M Memon, S Bazarbashi, Al Sedairy, Kadhi, Moreau, et al

**Project description**

Prospective Research Protocol- Sarcoma.

**Progress**

Active; slow accrual.

**24. Project title: Phase II Pilot Study Of Vincristine, Adriamycin, Actinomycin D, Ifosfamide Combination Chemotherapy In Ewing's Sarcoma. (RAC#2031-065)**

**Investigators:** M Memon, Raja, et al.

**Project description**

Prospective Research Protocol- Sarcoma.

**Progress**

Active; slow accrual.

**25. Project title: Pilot Trial Of Pre-Operative Chemo/ RT Using Xeloda And External Beam RT followed By Definite Surgery In Patients With Localized Rectal Carcinoma. (RAC#2011-031)**

**Investigators:** S Bazarbashi, et al.

**Project description**

Prospective Research Protocol-Colon/colorectal cancer

**Progress**

Follow-up only.

**26. Project title: First-Line Bevacizumab and Chemotherapy in Metastatic Cancer of the Colon or Rectum (International Study). (RAC#2041-082).**

**Investigators:** S Bazarbashi, et al.

**Project description**

Prospective Research Protocol- Colon/colorectal cancer.

**Progress**

Active.

**27. Project title: Autologous Peripheral Blood Stem Cell Transplantation With *In Vivo* Purging As An Alternate Stem Cell Transplantation Program For Patients w/ AML in 1<sup>st</sup> & 2<sup>nd</sup> Complete Remission w/no HLA Matched Related Donor. (RAC#2001-004)**

**Investigators:** F Mohareb, M Aljurf, E Sahovic, F Al Sharif, N Chaudhri, H Al Omar, A Shanqeeti, H Zahrani, M Morshed, S Zaidi, and P Seth.

**Project description**

Prospective Research Protocol- HSCT

**Progress**

Active.

**28. Project title: Induction Of Mixed Hemopoietic Chimerism In Patients Using Fludarabine, Low Dose Total Body Irradiation, Pheriperal Blood Stem Cell Infusion and Post Transplant In Immunosuppression w/Cyclosporin A & Mycophenolate Mofetil. (RAC#2001-051)**

**Investigators:** M Aljurf, H Al Omar, M Gyger, R Stuart, E Sahovic, Al-Homaidi.

**Project description**

Prospective Research Protocol- HSCT.

**Progress**

Active; very slow accrual.

**29. Project title: Prospective Randomized Trial Of Marrow Vs Filgrastim Mobilized Peripheral Blood Progenitor Cells In HLA- Matched Related Allogenic Transplant Wax W/Short Course Methotrexate & Cyclosporin A As Prophylaxis For Acute Graft vs. Host Disease. (RAC#1998-014).**

**Investigators:** M Aljurf, E Sahovic, M Gyger, R Stuart, F Al Sharif, N Chaudhri, and F Mohareb.

**Project description**

Prospective Research Protocol- HSCT.

**Progress**

Follow-up only.

**30. Project title: Prospective Study on combination immunotherapy for the treatment of aplastic anemia-Pilot Study. (RAC#2041-008).**

**Investigators:** H Al Zahrani, et al.

**Project description**

Prospective Research Protocol- Anemia.

**Progress**

Pending RAC approval.

**31. Project title: Acute Lymphoblastic Leukemia 1423 Protocol. (RAC# 2021-050)**

**Investigators:** E Sahovic, et al.

**Project description**

Prospective Research Protocol- ALL.

**Progress**

Follow-up only.

**RETROSPECTIVE STUDIES**

- M Abdelsalam, S Akhtar, I Maghfoor, A El Weshi, H Al Hussein, and Y Khafaga. Retrospective evaluation of primary central nervous system lymphoma. (RAC# 2051 034).
- M Abdelsalam, S Akhtar, I Maghfoor, A El Weshi, H Al Hussein, Y Khafaga, M Al Shabanah, and M Nabil Ahmad. Randomized phase II trial on primary chemotherapy with high-dose Methotrexate, alone or associated with high-dose Cytarabine, followed by response-and Age-tailored radiotherapy for immunocompetent patients with newly diagnosed primary central nervous system lymphoma. (RAC# 2051 058).
- S Akhtar, I Maghfoor, A El Weshi, M Rahal, M Abdelsalam, H Al Hussein, and I Janabi. Retrospective evaluation of high-dose chemotherapy and autologous stem cell transplantation in patients with Hodgkin's Lymphoma. (RAC# 2051 050).
- H Al Omar: 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# 990029)
- H Al Omar. Induction of mixed hematopoietic chimerism in patients using Fludarabine, low dose TVI, PBSC infusion and post transplant immunosuppression with Cyclosporine and Mycophenolate Mofetil. (RAC# 203022)
- H Al Omar. Evaluation of anti-tumor activity  $\gamma\delta$  T-cells in cancer patients.
- H Al Omar. Retrospective review: Leukemia relapses post stem cell transplantation- How does graft vs. host influence the pattern of relapse.
- S Akhtar, et al. Retrospective Evaluation of Primary Mediastinal Diffuse Large Cell and Hodgkin's Lymphoma. (RAC # 2051023).
- S Akhtar, et al. Retrospective evaluation of High-Dose Chemotherapy and Autologous Stem Cell Transplantation in Patient with Hodgkin's Lymphoma. (RAC # 2051050)
- S Akhtar, et al. Effect of radiation therapy on autologous peripheral blood stem cell (CD34+cells) collection in patients with relapsed or refractory diffuse large cell lymphoma and Hodgkin's lymphoma. (RAC # 2051024)
- S Akhtar, et al. Retrospective evaluation of primary central nervous system lymphoma. RAC # 2051034 (on going)
- S Akhtar, et al. Retrospective evaluation of ESHAP chemotherapy as a peripheral blood progenitor cells mobilization regimen in patients with Non Hodgkin's Lymphoma and Hodgkin's Lymphoma. RAC #2031008. (2003 – 2004)
- M Memon, et al. Retrospective review of outpatient management of adult Ewing's sarcoma. (RAC #2021061).
- M Memon, et al. Retrospective review of outpatient management of adult osteosarcoma. (RAC #2021062).
- M Memon, et al. Synovial Sarcoma at KFSH&RC, 1985-2000. Retrospective analysis of prognostic factors and treatment outcome. (RAC #202 1086).
- M Memon, et al. Sarcoma of the foot and ankle. A retrospective research project. (RAC #2021060).
- M Memon, et al. Phase II study of Vincristine Adriamycin, Actinomycin, Ifosfamide combination chemotherapy in Ewing's Sarcoma. (RAC #203 1065).
- M Memon, et al. Retrospective Evaluation of Adult Head and Neck Sarcoma (RAC #206 1073)
- F Hussain et al., Breast Cancer among Young Saudi Women

**PROSPECTIVE STUDIES**

- M Memon, et al. Weekly Carboplatin and Taxol with concurrent radiation therapy for locally advanced laryngeal and hypopharyngeal cancer. (RAC# 971 024).
- M Aljurf, et al, Alemtuzumab Treatment for Steroid-Refractory Acute Graft versus Host disease

## FUTURE RESEARCH DIRECTION

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- Promote well designed clinical/transitional research activities.
- Establish firm collaboration and break barriers with Research Center and other related organizations.
- Establish membership and collaboration with national, regional and international research working groups.
- Expand and maximize utilization of available database for certain tumor sites in research direction and bench marking
- Establish a refresher course for the Clinical Research Coordinators to achieve CCRP certification.
- Establish more international multicenter clinical research trials in collaboration with myriads of cooperative groups.
- To host an international symposium on hematological malignancies

## PUBLICATIONS

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- Successful Treatment of Hepatic Venous Occlusive Disease after Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation by early administration of a short course of Methylprednisolone: *BMT* (2007) 00, 1-5.
- Hepatotoxicity induced by horse AYG and reversed by rabbit ATG: a case report. *Journal of Medical Case Reports* 2007, 1:35 doi:10.1186/1752-1947-1-35. K. Al-Anazi, M. Aljurf, F. Al-Sharif, H. Al Omar, A. Alami, F. Farooq.
- Pattern of electrolyte abnormalities among cancer patients referred to palliative care: A review of 750 patients. *Progress in Palliative Care*, 15(4): 182-186; 2007. S. Alsirafy, M. Al-Shahri, A. Hassan, M. Hidayatullah, H. Ghanem.
- Death, Dying and Burial Rites in Islam. *European Journal of Palliative Care*, 14(4): 164-167; 2007. M. Al-Shahri, N. Fadul, A. Elsayem.
- Expression of B7-H1 in breast cancer patients is strongly associated with high proliferative Ki-67 expressing tumor cells. *Int J Cancer*. 2007 Aug 15;121(4):751-8. H. Ghebeh, A. Tulbah, T. Al-Twegieri, S. Dermime.
- Being 40 or younger is an independent risk factor for relapse in operable breast cancer patients: The Saudi Arabia experience. *BMC Cancer*. 2007 Dec 5;7(1):222. N. Elkum, S. Dermime, D. Ajarim, A. Al-Zahrani, A. Alsayed, A. Tulbah, O. Al-Malik, M.

Alshabanah, A. Ezzat, T. Al-Twegieri.

- Improvement in histologic response but not survival in Osteosarcoma patients treated with intensified chemotherapy: A randomized phase III trial of the European Osteosarcoma Intergroup. *JNCI*, Vol. 99, Issue No. 2, 17 January 2007. I. Lewis, M. Nooij, J. Whelan, M. Sydes, R. Grimer, P. Hogendoorn, M. Memon, S. Weeden, B. Uscinska, M. Glabbeke, A. Kirkpatrick, E. Hauben, A. Craft, A. Taminiau.
- Volumetric staging (VS) is superior to TNM and AJCC staging in predicting outcome of head and neck cancer treated with IMRT. *Acta Oncologica*, 2007; 46, 386-394. G. Studer, U.M. Lutolf, M. Al-Bassiouni, V. Rousson, C. Glanzmann.
- Primary refractory Hodgkin's Lymphoma: Outcome after high dose chemotherapy and autologous SCT and impact of various factors on overall and event free survival. A single institution of 60 patients. *Bone Marrow Transplantation*, 2007 October;40(1) 651-1. Epub 2007 Jul 30. S. Akhtar, A. El-Weshi, M. Abdelsalam, H. Hussaini, M. Rahal, I. Maghfoor.
- T-cell/histocyte-rich-B-cell Lymphoma: Clinical presentation, management and prognostic factors; report of 61 patients and review of literature. *Leuk Lymphoma*, 2007 September 48(9): 1764-73. A. El-Welshi, S. Akhtar, W.A. Mourad, D. Ajarim, M. Abdelsalam, Y. Khafaga, S. Bazarbashi, I. Maghfoor.
- Sensitive caring for Muslim patients. *AAHPM Bulletin* Spring 2007. M. Al-Shahri.

## PRESENTATIONS/CONGRESS PROCEEDINGS

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- Autologous HSCT for Multiple Myeloma and King Faisal Cancer Centre Experience, Dr. F. Al-Mohareb, Presented at Update of Oncology 2007, KFSH&RC, Jeddah. 28 February 2007.
- Radiotherapy for Early Breast Cancer: An Update, Dr. M. Al-Shabanah, Oncology Update 2007, Expanding Horizons, KFSH&RC, Jeddah, 28 Feb. 2007
- New Technologies in Lung Cancer Radiation Therapy, Dr. A. Al-Hebshi, Oncology Update 2007, Expanding Horizons, 28 February 2007
- Approach to challenging cancer pain, Dr. M. Al-Shahri, Dammam Central Hospital, Dammam. Feb 2007
- Role of Home Health Care in Palliative Care, Dr. M. Al-Shahri, First Home Health Care Meeting, Al-Madinah (In Arabic). Feb 2007
- Psychosocial & Spiritual issues in cancer, Dr. M. Al-Shahri, Oncology Update 2007, KFSHRC, Jeddah. Feb 2007

- Palliative Treatment of Cancer Pain, Dr. M. Al-Shahri, Saudi Colorectal Surgery Forum, KFSHRC, Riyadh. Mar 2007
- Palliative Care in Saudi Arabia, Dr. M. Al-Shahri, King Khalid National Guard Hospital, Jeddah. May 2007
- Palliative Care for Muslim patients, Dr. M. Al-Shahri, Palliative Medicine Seminars for Fellows, KFSHRC, Riyadh. Aug 2007
- Cancer pain management, Dr. M. Al-Shahri, Palliative Medicine Seminars for Fellows, KFSHRC, Riyadh. Aug 2007
- Breaking bad news, Dr. M. Al-Shahri, Palliative Medicine Seminars for Fellows, KFSHRC, Riyadh. Aug 2007
- Philosophy of palliative care, Dr. M. Al-Shahri, Second Regional Congress of Cancer and Blood Diseases of Childhood, Amman, Jordan. Sept 2007
- Pediatric Cancer Pain Management, Dr. M. Al-Shahri, Second Regional Congress of Cancer and Blood Diseases of Childhood, Amman, Jordan. Sept 2007
- Management of nausea & vomiting, Dr. M. Al-Shahri, Palliative Medicine Seminars for Fellows, KFSHRC, Riyadh. Oct 2007
- Neuropathic pain I, Dr. M. Al-Shahri, Palliative Medicine Seminars for Fellows, KFSHRC, Riyadh. Oct 2007
- Neuropathic pain II, Dr. M. Al-Shahri, Palliative Medicine Seminars for Fellows, KFSHRC, Riyadh. Nov 2007
- Bone pain, Dr. M. Al-Shahri, Palliative Medicine Seminars for Fellows, KFSHRC, Riyadh. Nov 2007
- Intractable cancer pain, Dr. M. Al-Shahri, Palliative Medicine Seminars for Fellows, KFSHRC, Riyadh. Nov 2007
- Palliative Care in Gyne Oncology, Dr. M. Al-Shahri, OB/Gyne residents seminars, KFSHRC, Riyadh. Dec 2007
- Management of selected Non pain symptoms in the terminally ill patients, Dr. A. Hassan, SEMCO-ESMO-ACOD conference with EASO (Recent Advances in Oncology), Alexandria, Egypt. Dec 2007
- End of life care, a holistic approach, Dr. M. El-Foudeh, Oral presentation, 11<sup>th</sup> Annual International Clinical, ESMCO-ESMO-ACOD, Recent Advance in Oncology, Oncology – Alexandria, Egypt, December 2007
- Cancer pain management, Dr. M. El-Foudeh, Oral presentation, The 3<sup>rd</sup> International Medical Oncology Conference, Salah – Oman, August 2007
- How to established palliative care services, Dr. M. El-Foudeh, Oral presentation, The 3<sup>rd</sup> International Medical Oncology Conference, Salah – Oman, August 2007
- Quality care at the end of life in cancer patients, Dr. M. El-Foudeh, Oral Presentation International Conference, Advances in Clinical Oncology, Al Ain, UAE, February 2007
- Cancer pain: A significant problem through the world, Dr. M. El-Foudeh, Oral presentation, Cancer Pain Master Class Symposium, International Conference, Advances in Clinical Oncology, Al Ain, UAE, February 2007
- End of life care (person in the patient), Dr. M. El-Foudeh, Oral presentation, Cancer Pain Master Class Symposium, International Conference, Advances in Clinical Oncology, Al Ain, UAE, February 2007
- Cancer Pain Management, Dr. M. El-Foudeh, Oral presentation, Oncology Update 2007 Expanding Horizons, KFSH&RC, Jeddah, Saudi Arabia, February 2007
- End of life care (nursing issues), Dr. M. El-Foudeh, Oral presentation, Oncology Update 2007 Expanding Horizons, KFSH&RC, Jeddah, Saudi Arabia, February 2007

## ABSTRACTS

### 32. Prevalence and risk factors of developing Bronchiolitis Obliterans (BO) in post allogenic bone marrow transplant (BMT) patients. International Congress on Bone Marrow and Stem Cell Transplantation. 13-15 November 2007.

**Investigators:** M. Khalid, A. Al Mobeireek, M. Al Jurf, S. Al Jawder, F. Al Mohareb, S. Saleemi, N. Chaudhri.

#### Introduction

Bronchiolitis Obliterans (BO) is a frequent pulmonary complication in post bone marrow transplant (BMT) patients. In our review of post BMT patients at King Faisal Specialist Hospital & Research Centre (KFSH & RC), we tried to establish the prevalence in our patient population and the factors which could be associated with the development of BO in our post BMT patients.

#### Method

Retrospective review of all post BMT patients from January 1995 – December 2005 was done. Their pre and post BMT pulmonary function test (PFT) were reviewed. Standard American Thoracic Society (ATS) Guidelines were used to establish the diagnosis of obstructive airway disease (OAD). Patients with existing OAD were excluded from the study. Patients underlying diseases and demographic data and its impact on

development of OAD were recorded, as well as presence of graft-versus-host-disease (GVHD) and cytomegalovirus (CMV) and the association of OAD was recorded. Of 580 transplants done from January 1995 – December 2005, 158 patients had PFTs done. 53 patients were excluded for either having an existing OAD, or did not have post BMT PFTs, 105 patients were included in the study.

### Results

In our review 60/105 (57.14%) patient developed OAD with equal male to female ratio (30 males and 30 females), reflecting a much higher prevalence of OAD in our patient population compared to other centers were reported prevalence is around 15%. In our review OAD was frequently associated with acute lymphocytic leukemia (ALL), acute myelocytic leukemia (AML) affecting 69.5% and 56.6% patients respectively. Blood groups with Rh+ antigen (ABO+, AB+) had higher association with OAD compared to Rh- blood groups, patients with positive CMV antigenemia 59/104 (56.73%) had OAD, chronic GVHD was associated with 69.7% and acute GVHD was associated with OAD in 68.7% patients. No beneficial response to immunosuppressive and steroid therapy was noticed. Despite treatment all patients with OAD showed progressive decline in their OAD parameters.

### Conclusion

Our study identified the prevalence of OAD in post BMT patients population to be 60/105 (57.14%) much higher in our population than reported by other centers. Most likely this is due to a lack of PFTs in all post BMT patients which could have overestimated our prevalence of OAD (BO). Underlying diagnosis ALL and AML were frequently associated with OAD as well as blood groups with Rh+ antigen had very high prevalence, chronic and acute GVHD and presence of CMV infection were strong predictor of future development of OAD (BO). No beneficial response noted on OAD with the existing treatment (immunosuppressive therapy and steroids).

### Clinical Significance

Further studies are needed to evaluate these risk factors and new modalities of treatment may be needed to prevent and treat this life threatening post BMT complication.

**33. Early predictor of Bronchiolitis Obliterans (BO) In Post Bone Marrow Transplant (BMT) Patients. International Congress On Bone Marrow And Stem Cell Transplantation. 13-15 November 2007.**

**Investigators:** M. Khalid, N. Chaudhri, A. Al Mobeireek, S. Al Jawder, F. Al Mohareb, S. Saleemi, M. Al Jurf.

### Introduction

Bronchitis Obliterans (BO) is a frequent pulmonary complication in post bone marrow transplant (BMT) patients. It is usually a part of systemic manifestation of graft-versus-host-disease (GVHD) but could also be an isolated pulmonary complication. An early detection of airway obstruction on pulmonary function test (PFTs) may suggest developing BO and may help in early management intervention to prevent development of advanced BO syndrome with respiratory failure.

### Objectives

To establish the early predictors of development of obstructive airway disease (OAD) in post BMT patients.

### Materials and Method

King Faisal Specialist Hospital and Research Centre, a tertiary care center performs an average of 200 bone marrow transplant (BMTs) /year. Ours is a study of review of 10 years pre and post BMTs, PFTs. All patients from January 1995 to December 2005 were included in the study. Standard American Thoracic Society (ATS) Guideline for changes in PFTs parameter was used as a significant result.

### Results

Of 580 transplants done from January 1995- December 2005, 158 patients had PFTs done. Of those, 89 were excluded (20 patients died early post BMT, 28 had OAD on pre BMT and 41 patients who had single post BMT PFT). The remaining 49 patient who had serial PFTs were investigated to find if there was an early predictor of development of obstructive airway disease (OAD) on their PFTs. Early in the post BMT, no significant change occurred in PFT parameters (FEV1, MEF 25-75, RV, TLC) except of RV/TLC ratio. (mean increase in value was 10.88% (from 108-118.88%) was significant on their first post BMT, PFT. Subsequent PFTs in our statistical analysis suggested patients with abnormal RV/TLC on their first post BMT also developed a progressive decline in other parameters of OAD like ↓MEF, ↓ FEV1, ↑TLC and also further deterioration of RV/TLC ratio.

### Conclusion

Our study identified very early objective sign of developing BO in the form of airflow limitation with increase RV/TLC ratio which was a strong predictor of future development of OAD and developing BO. Conventionally acceptable

changes of OAD like ↓FEV1 (Forced Expiratory Volume in 1 second) and ↓MEF (Mid expiratory flow) and ↓TLC took much longer to manifest developing OAD. Prospective studies maybe needed to further evaluate this evidence and also if the early management intervention with changes in RV/TLC ratio has beneficial outcome in terms of delaying development of OAD and the long term prognosis of BO.

**34. High Rate Of Remission And Survival Outcome Of Adult Acute Lymphoblastic Leukemia Using Dexamethasone In Intensification And Maintenance: Results Of KFSH&RC 1423 Protocol. International Congress On Bone Marrow And Stem Cell Transplantation. 13-15 November 2007.**

evidence of leukemia in BM on d-14 received Fludarabine and Ara-C (FA) high dose salvage. Consolidation with High Dose Ara-C was given upon recovery. Patients with no high risk features (39%) then received 2 monthly Intensification of CHOD followed by Maintenance of monthly VCR plus Dexamethasone (D), weekly MTX and daily GMP.

Patients younger than 50 years were offered matched allogeneic stem cell transplantation, when available, if they had any of the high risk features at presentation or if day-14 BM showed residual leukemia or required more than 5 weeks to achieve CR. Seventy three patients (60.3%) had high risk features at presentation

**Significance between Pre and Post Transplant Measurements:**

	FEV1		MEF		RV		TLC		RV/TLC	
	pre	post	pre	post	pre	post	pre	post	pre	post
Mean	92.17	91.63	98.05	95.82	100.70	104.89	91.63	88.27	108.91	118.88
Variance	64.82	84.98	837.26	1316.65	380.84	628.04	99.01	127.4	501.44	1162.64
Observation	49	49	49	49	47	47	47	47	47	47
Pearson Correlation	0.75	-	0.57	-	0.29	-	0.70	-	0.43	-
df	48	-	48	-	46	-	46	-	46	-
t Stat	0.61	-	0.5	-	-1.06	-	2.79	-	-2.15	-
P (T<t) one-tail	0.27	-	0.31	-	0.15	-	0.0038	-	0.0185	-

**Investigators:** M. Said, M. Al Jurf, F. Al Mohareb, F. Al Sharif, H. Al Zahrani, K. Al Anazi, A. Saleh, M. Bakr, A. Nassar, S. Ahmed, A. Abdulwahab, A. Al Shehri, H. Al-Tanbal, E. Colcol, I. El-Hassan, F. Hussain, N. Chaudhri.

Between February 2002 and June 2007 a total of 121 patients with Acute Lymphoblastic Leukemia were treated at King Faisal Specialist Hospital & Research Center (KFSHRC), Riyadh.

All patients (age < 50 years) received induction therapy with 1423 (Adriamycin (H) d1-3, Cyclophosphamide (C) day-1, Vincristine (VCR) d-1, 8, 15, & 22 and L-Asparaginase d-5, 7, 9, & 12). Those who had

(61%) (age > 30, extra-medullary disease, abnormally high WBCs > 30k in B- and > 100k in T-ALL, high risk cytogenetics including BCR/ABL, t(4;11) and complex karyotyping).

**Immunophenotyping**

73 (60.3%) pre B, 32 (26.5%) T-ALL, LBL/ALL in 13 patients, 70% normal cytogenetics and the majority of others carried poor risk cytogenetics. 111 patients (91.7%) achieved CR by d 28-35, although only 12 (10%) of them required an additional one salvage course with FA on d-14 due to persistence of leukemia (>5%). Treatment related mortality (TRM) was significantly low (3%).

Those who achieved CR had an overall survival of 43.6

% at 50 months. Three year OS of those who achieved CR was 59 + 8%, disease free survival (DFS) was 41.2 + 6%. No correlation between risk factors and rate of remission on d-14 or d-28. D-14 remission favored better overall survival ( $p=0.02$ ) while age group >30 years had significantly shorter median survival ( $p < 0.05$ ). Patients younger than 20 years had better OS and DFS than older ones ( $p= 0.056$  and  $0.049$  respectively). No impact of other risk factors or transplantation on OS or DFS was found. Interestingly, CNS relapses after transplantation was significantly lower than chemo only arm, over the same time period ( $p= 0.05$ ).

#### Conclusion

The KFSHRC 1423 protocol is an effective remission induction regimen and addition of Dexamethasone to maintenance for adults was well tolerated and effective in maintaining remission.

#### 35. 4. Immunomodulation By Donor Lymphocyte Infusion For Treatment Of Relapse After Allogeneic Stem Cell Transplantation. International Congress On Bone Marrow And Stem Cell Transplantation. 13-15 November 2007.

**Investigators:** F. Al Mohareb, M. Said, N. Chaudhri, F. Al Sharif, H. Al Zahrani, K. Al-Anazi, A. Saleh, M. Bakr, A. Nassar, S. Ahmed, A. Abdulwahab, A. Al Shehri, E. Colcol, R. Belkhedim, F. Hussain, M. Al Jurf.

Donor leukocyte infusion (DLI) represents a viable option for management of relapse after Allogeneic Bone Marrow Transplantation (BMT). However, efficiency in achieving and maintaining remission may differ from one disease to another depending upon many variables.

We evaluated the effect of DLI in 72 patients (43 CML, 15 AML, 5 ALL, 4 MDS, 3 NHL, 1 SAA) over the last 15 years (1993-2007).

The overall survival of the whole cohort was 35.9% at 100 month with a median survival of 22 months and Disease free survival (DSF) of 45.1%. 11.3% of the evaluable patients experienced Acute GVHD grade I/II and only 7% developed extensive chronic GVHD.

The Event Free Survival of the whole cohort was 15.5%. However, patients with more indolent diseases like CML had the best outcome with Complete Remission (CR) of 76.7% and disease free survival (DFS) of 53.5%. In addition, all the 3 patients with NHL achieved CR and remained disease free, indicating that DLI may be

more effective as an immunotherapy when given in more indolent diseases.

On the contrary, DLI was not effective in all the 5 patients with ALL. However, 33.3 % of relapsing AML patients achieved CR and remained Disease free.

Patients who relapsed early (< 6month) after transplantation had the worst outcome in terms of remission and survival.

Most of post-DLI failures were related to either progression of disease or development of extramedullary disease, indicating that DLI is not effective in extramedullary relapse or relapse prevention.

#### 36. Correlation Of Endoscopic And Histological Grading In Acute Graft-Versus-Host Disease (GVHD). International Congress On Bone Marrow And Stem Cell Transplantation. 13-15 November 2007.

**Investigators:** M. Khan, H. Al-Ashgar, M. Al Kahtani, M. Al Fadda, M. Al Jurf, N. Chaudhri.

#### Background and Study Aim

Graft-versus-host disease (GVHD) of the gastrointestinal tract is a major cause of morbidity and mortality after allogeneic bone marrow or stem cell transplantation. Whether macroscopic endoscopic grading predicts the histological staging of GVHD remains controversial. We reviewed the grading of endoscopic images in patients who were reported to have definite histological diagnosis of GVHD. This early endoscopic diagnosis could direct us to start specific therapy earlier and avoid the complication of endoscopic biopsies in severely thrombocytopenic patients.

#### Patients and Methods

41 patients, who had definite histological diagnosis of acute GVHD, had undergone gastrointestinal biopsies from gastric (34), duodenum (7) and sigmoid (32). Endoscopic images of these patients were reviewed retrospectively since 2003 by 2 expert endoscopists. The endoscopic appearances of stomach, duodenum and sigmoid were staged in four grades, according to the severity of macroscopic pictures. Correlations of four endoscopic grading (Brand RE et al, 1998) with four histological grading (McDonald and Sale, 1984) were compared, to determine the diagnostic accuracy in assessing the severity of GVHD. Statistical analysis of relationship was measured by Cohen's Kappa measure of agreement.

## Results

As the measure of agreement, grading between two techniques, endoscopic and histological, the Gastric measure was 0.579, moderate agreement ( $p < 0.0001$ ) and sigmoid was 0.219, fair agreement ( $p < 0.010$ ). Duodenal biopsies numbers were too small to get a significant relationship.

## Conclusion

Quite accurate early diagnosis and grading of acute GVHD could be obtained by the endoscopic images especially from the gastric and sigmoid, but histological evaluation is mandatory to exclude other causes of inflammation which give similar endoscopic images before committing for the final diagnosis of GVHD.

### 37. Favorable Outcome Of Fludarabine And Cyclophosphamide As A Bone Marrow Transplantation Conditioning Regimen For Patients With Severe And Very Severe Aplastic Anaemia. EBMT Congress, Lyon, France. 25-28 March 2007.

**Investigators:** H. Al-Zahrani, F. Al-Mohareb, F. Al-Sharif, H. Al-Omar, A. Al-Shanqeeti, N. Chaudhri, E. Sahovic, S. Zaidi, A. Saleh, K. Al-Anazi, A. Abdulwahab, A. Al-Shahri, M. Morshed, A. Nassar, M. Aljurf.

### 38. Application Of Free Flow Electrophoresis For Proteomic Analysis Of Plasma, Serum And Bone Marrow Of Chronic Myeloid Leukemia And Aplastic Anemia. HUPD 6<sup>th</sup> Annual World Congress for Proteomics, Seoul, Korea. 06-10 October 2007.

**Investigators:** M. Al Mohanna, M. Aljurf, M. Nissum, M. Al Eid, F. Al Mohareb, N. Chaudhri, F. Al-Sharif, et al.

### 39. Reduction in $\lambda\delta$ T-Cell Function and Granzyme B Gene Polymorphism in Newly Diagnosed Breast Cancer Patients, Expansion with Zoledronic Acid Partially Compensate for this Deficiency. 36th Annual Scientific Meeting of ISEH Society for Hematology and Stem Cells, Congress Center Hamburg, Germany. 28-30 September 2007.

**Investigators:** A. Gaafar, M. Aljurf, A. Al-Sulaiman, A. Iqniebi, A. Al-Sayed, M. Pulicat, H. Al-Zahrani, F. Al-Sharif, et al.

### 40. 9. Synergistic effect of Fox3 Plus regulatory T cells and T cells expressing B7-H1 in the immune escape of breast cancer patients. World Immune Regulation Meeting, Switzerland, Abstract 233, Page 217. 11-15 April 2007.

**Investigators:** H. Ghebeh, E. Barhoush, A. Tulbah, C. Leher, T. Al-Twegieri, S. Dermime.

### 41. Prospective Phase II Study of Neo-adjuvant Doxorubicin followed by Cisplatin/Docetaxel in locally advanced breast cancer a 5 years of follow up. Journal Clinical Oncology, Vol. 25, No. 18S, Abs.;10574. 2007

**Investigators:** D. Ajarim, M. Rahal, A. Alsayed, M. Alshabanah, A. Tulba, O. Almalik, G. El-Husseiny, A. Ezzat and T. Al-Twegieri.

### 42. Triple-negative breast cancer. A clinicopathologic study of 113 cases and comparison with 55 cases with triple positive breast cancer: A matched-control analysis. Journal Clinical Oncology, Vol. 25, No. 18S, Abs.;21119. 2007

**Investigators:** El Weashi, A. Tulbah, A. Al sayed, T. Al-Twegieri, M. Alshabanah, O. Almalik, D. Ajarim.

### 43. Being 40 or younger is an independent risk factor for relapse in operable breast cancer patients: The Saudi Arabia experience. 7th Scientific Meeting of the International Epidemiology Association Abstract 69. 28 November 2007.

**Investigators:** N. Elkum, S. Dermime, D. Ajarim, A. Al-Zahrani, A. Alsayed, A. Tulbah, O. Al-Malik, M. Alshabanah, A. Ezzat, T. Al-Twegieri.



**KING FAISAL HEART INSTITUTE**



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# KING FAISAL HEART INSTITUTE

The King Faisal Heart Institute (KFHI) is committed to excellence in patient care, teaching, and research. Its mandate includes research into the current and future effects of cardiovascular diseases in Saudi Arabia. Its primary objectives are to increase the general scientific knowledge of cardiovascular diseases including their epidemiology, risk and risk factors, prevention, detection and diagnosis, treatment and prognosis, and to initiate evidence-based, cardiovascular programs.

*Director*  
**Charles C. Canver, MD, FACS, FACC,  
FCCP, FCCM**

During 2007 the KFHI had 39 approved/ongoing research projects. These projects included retrospective records review and analysis, registries, interventional research, diagnostic research, basic research, and animal studies. All sections of the KFHI are involved in research with the distribution as follows: adult cardiology = 6, adult cardiovascular surgery = 5, pediatric cardiology = 11, pediatric cardiovascular surgery = 12, databases which include adult and pediatric surgery or adult and pediatric cardiology = 5.

The KFHI continues to develop its 5-year Strategic Research Plan (SRP) which is designed to develop and sustain significant and internationally-acknowledged research in several thematic areas that are relevant to the high incidence of cardiovascular diseases in the Kingdom. The KFHI plans to significantly increase its research capacity and capability over the next five years towards achieving even greater international recognition for its high caliber research.

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## RESEARCH PROJECTS

- 1. Project title: The applicability of the "Risk Adjustment for Congenital Heart Surgery (RACHS-1)" scoring system for stratification of probability of mortality following congenital heart surgery in an international heart institute. RAC #: 2071046**

**Investigator/s:** Fareed Khouqeer, Ahmad Bin Sallehuddin, Bahaaldin Al Soufi

### Project description

The aims of this Study were to:

- determine the mortality rates following congenital surgery at the KFHI.
- rate the above patients according to the RACHS-1 scoring system.
- compare the scores from the RACHS-1 scoring system with mortality rates at the KFHI.

### Progress

Data collection was completed in December 2007. The data analysis revealed a positive and progressive relationship between the RACHS-1 scoring system and surgery outcome of in-hospital mortality at the KFSH&RC. It was concluded that the RACHS-1 scoring system has excellent power to reasonably predict mortality in a non-North American, non-European heart institute and it can discriminate between different categories of congenital heart surgery based on that predicted risk.

- 2. Project title: Diagnostic Outcome Trial in Heart Failure (DOT-HF). RAC #: 2071039**

**Investigator/s:** Majid Al Fayyadh, Bandar Al Ghamdi, Yaseen Mallawi, Jihad Al Buraiki, Waleed Manea

### Project description

The primary objective of this Study is to demonstrate a reduction in the combined endpoints of HF hospitalizations and all-cause mortality in HF subjects managed with standard clinical assessment and using OptiVol® Fluid Status Monitoring with Cardiac Compass Report ("Access Arm") compared to HF subjects managed with standard clinical assessment ("Control Arm").

### Progress

This Study was approved December 2007; no patients were enrolled as of 31 December 2007.

- 3. Project title: Transcatheter Closure of Patent Ductus Arteriosus in Patients  $\leq$  8 kg. RAC #: 2071021**

**Investigator/s:** Mansour Al Joufan, Khalid Al Omran, Ahmed AlOmrani

### Project description

Patent ductus arteriosus (PDA) is a frequently seen congenital heart disease. Its transcatheter closure has become the treatment of choice in children and adults. However, the device closure of PDA in children with low weight is still challenging, with a high rate of complications. This Study will report the KFSH&RC experience with transcatheter closure of PDA for children with weight  $\leq$  8 Kg. The results will improve our knowledge of the effectiveness and safety of device PDA closure in patients with low weight.

### Progress

Data collection is ongoing.

- 4. Project title: Can Echocardiography Replace Cardiac Catheterization in the Pre-Operative Evaluation of Tetralogy of Fallot?. RAC #: 2071015**

**Investigator/s:** Ahmed Bin Sallehuddin, Majid Al Fayyadh, Mansour Al Joufan, Ziad Al Issa, Khaled Al Omran, Faraz Baig

### Project description

This study will evaluate the accuracy of two-dimensional echocardiography in defining the coronary and pulmonary artery anatomies in patients planned for surgical correction of Tetralogy of Fallot. It will compare its accuracy with angiography and findings at surgery.

### Progress

Data collection is ongoing.

- 5. Project title: Pulmonary Atresia with Intact Ventricular Septum: Initial Management and Follow-up (Retrospective Review). RAC #: 2071005**

**Investigator/s:** Mansour Al Joufan, Ahmad Bin Sallehuddin, Saud Al Oufi, Ahmad AlOmrani, Amal Silmi

#### Project description

Pulmonary Stresia with Intact Ventricular Septum (PAIVS) is an uncommon congenital cardiac anomaly with remarkable morphologic variability, affecting not only the pulmonary valve but also the tricuspid valve, the right ventricular cavity and the coronary arteries. With advances in interventional techniques and congenital heart surgery, the management of PAIVS continues to evolve. However, the criteria for determining an adequate procedure remains unclear. The objectives of this retrospective review are to: a) Describe the initial management and mid-term results of interventional and surgical repair of PAIVS at a single center (KFSHRC), and b) Compare different strategies of management of PAIVS and their impact on right ventricular growth and prognosis.

#### Progress

Data collection is ongoing.

#### 6. Project title: E-Select Registry. RAC #: 2061077

**Investigator/s:** Fawaz Al Turki, Walid Rafeh, Jehad Al-Buraiki, Walid Hassan, Hani Al-Sergani

#### Project description

This multi-center observational study (500 centers worldwide) is collecting national profiles and epidemiological data on patients who received Cordis Sirolimus-Eluting Stents (SES). The aims of this post-marketing study are to:

- a. investigate the long-term effects, safety and performance efficiency of the SES in routine clinical practice;
- b. assess the frequency and duration of acute or chronic coronary syndrome related events;
- c. describe and measure the incidence of acute, sub-acute and late stent thrombosis and major adverse cardiac events (MACE);
- d. identify the predictors of acute, sub-acute and late stent thrombosis and MACE;
- e. analyze the stent performance data in patient sub-populations for diabetes, in-stent

restenosis, acute myocardial infarction & multi-vessel coronary disease.

#### Progress

This Study was approved in July 2007; forty patients have been enrolled.

#### 7. Project title: PANORAMA: An Observational Study. RAC #: 2061075

**Investigator/s:** Majid Al Fayyadh, Manal Al-Harithi, Yaseen Mallawi, Waleed Manea, Bandar Al-Ghamdi

#### Project description

This Study involves the collection of epidemiological data on patients who have Medtronic implantable pulse generators and implantable cardioverters/defibrillators.

The aims of this post-marketing study are to:

- a. investigate the long-term operation of the devices and device features;
- b. assess the frequency and duration of heart-failure related hospitalizations;
- c. analyze temporal aspects of cardiovascular events and symptoms;
- d. describe the incidence and prevalence of ventricular and atrial arrhythmias;
- e. associate cardiovascular events and symptoms with device data and diagnostics;
- f. determine programming preferences considering physical assessment variables and pathologies;
- g. build a prognostic model of time to death by using population baseline variables as predictors.

#### Progress

Fifty-seven patients have been enrolled.

#### 8. Project title: NT-Pro Brain Natriuretic Peptide (NT proBNP) Levels in Neonates With and Without Cardiac Disease – a New Method to Detect Cardiac Causes of Respiratory Insufficiency in Neonates. RAC #: 2061068

**Investigator/s:** Ghassan Siblini, Mahmood Al-Asmi, Jalaluddin Bhuiyan, Majid Al-Fayyadh, Avedis Kaloghlian, Ziad Bulbul

**Project description**

This prospective randomized, stratified study will measure and assess blood NT-proBNP levels which are elevated only in full-term and premature neonates who are oxygen or ventilator dependant due to hemodynamically significant large left-to-right shunts. Determination of NT-Pro-BNP levels will allow physicians to differentiate cardiac from non-cardiac causes of oxygen/ventilator dependence when an echocardiographic diagnosis may not be available.

The aims of the study are to confirm the normative levels of NT-proBNP and Troponin-T in a sample of healthy Saudi neonates and premature infants and to compare these values to NT-proBNP levels in premature infants with congenital heart disease.

**Progress**

Twenty patients, 5 cases and 15 controls, have been enrolled. Enrollment is ongoing and expected to be completed in December 2008.

**9. Project title: The Impact of Palliative Procedures on the Growth of Pulmonary Arteries in Pulmonary Atresia with Ventricular Septal Defect. RAC #: 2061041**

**Investigator/s:** Akram Allam, Ahmad Bin Sallehuddin, Mansour Al Joufan, Ziad Issa, Mohammad Kandeel

**Project description**

This retrospective study will evaluate the impact on the growth of the neo-pulmonary artery and major aorto-pulmonary collateral arteries following various palliative approaches in patients with pulmonary atresia with ventricular septal defect, and will identify the most successful method.

**Progress**

The investigators have reviewed the charts of approximately 100 patients and have collected data from 49, including data from catheterization films. Data continues to be collected from medical records, catheterization films, and surgery reports.

**10. Project title: Prospective Trial of Endoscopic versus Conventional Vein Harvesting Techniques for CABG: Morphology and Post-Operative Outcome. RAC #: 2061034**

**Investigator/s:** Charles Carver, Sajjad Yousafzai, Aly Al Sanei, Emad Bukhari, Fouad Al Dayel

**Project description**

This prospective study will assess whether minimally invasive endoscopic harvesting of the saphenous vein performed at the KFSH&RC reduces harvesting site tissue damage and morbidity. The study will also compare the histological properties of saphenous veins harvested conventionally with saphenous veins harvested endoscopically.

**Progress**

This study was approved by the RAC in April 2007, however enrollment has been delayed as the former Principal Investigator left the KFSH&RC.

**11. Project title: Early and Long-term Outcomes and Follow-up of Mechanical Valve Replacement in Patients Less than 15 Years of Age. RAC #: 2061029**

**Investigator/s:** Elias Saad, Ahmed Moussa, Avedis Kalloghlian, Zohair Al Halees

**Project description**

This retrospective review will analyze the data of patients, up to 15 years of age, who underwent mechanical valve prosthesis implantation procedures. Three groups will be studied based on their age: Group I: 2 years of age and younger, Group II: 2 to 5 years, and Group III: 5 to 15 years. The Study will document long-term clinical outcomes and valve-associated complications.

**Progress**

Two hundred twenty-eight MRNs have been identified as patients appropriate for this Study. Data collection is ongoing.

**12. Project title: Are Palliative and Reconstructive Procedures Effective in Promoting Growth of Pulmonary Arteries in Cases of Pulmonary Atresia (PA), Ventricular Septal Defect (VSD) and Major Aorto-Pulmonary Collaterals (MAPCs)? RAC #: 2061018**

**Investigator/s:** Fareed Khouqeer, Ziad Issa, Ghassan Siblini

**Project description**

This retrospective study is reviewing and analyzing all consecutive cases of PA with VSD and MAPCs treated at the KFSH&RC over the last 10 years. A detailed description of the pulmonary artery anatomy, the abnormal arborization and the collaterals is being done for each case, based on cardiac catheterization findings. The influence of PA morphology and other factors on the final outcomes are being studied, as well as the different palliative and reconstructive procedures offered to patients and the effect of each approach.

**Progress**

Data has been collected from catheterization cines on 61 patients and the associated medical records data is being reviewed.

**13. Project title: Redo Coronary Artery Bypass: Why so Infrequent? RAC #: 2061002**

**Investigator/s:** Fareed Khouqeer, Mohammed Kandeel

**Project description**

This retrospective chart review studied the redo coronary artery bypass graft (CABG) procedures performed at the KFSH&RC. The project reviewed the techniques used and attempted to identify the factors which may affect the frequency of 'Redo-CABG' surgeries.

**Progress**

The study was completed in October 2007. The results showed that the incidence of CABG-redo procedures at the KFHI was low and therefore did not provide enough data to allow for meaningful analysis of factors which may affect the need for the procedure (re-CABG).

**14. Project title: Clopidogrel and Hemorrhage in Coronary Artery Bypass Grafting (CABG): A Retrospective Study RAC #: 2061004**

**Investigator/s:** Shahid Khan, Aly Al-Sanei, Charles Canver, Barima Afrane

**Project description**

This retrospective study will evaluate KFSH&RC patients

who received Clopidogrel (an anti-platelet agent) and who underwent CABG. The aims are to determine the effect of Clopidogrel on blood loss during surgery, and to describe Clopidogrel-associated morbidity and mortality.

**Progress**

Two hundred seven patient's records that meet the study criteria have been identified; data has been collected from approximately 25%.

**15. Project title: Pilot Study: Evaluation of a Modified Technique of Heterotopic Heart Transplantation in Dogs and Rats. RAC #: 2060019**

**Investigator/s:** Charles Canver, Barima Afrane

**Project description**

Using the dog as an animal model, this feasibility study evaluated a reproducible and easy to manage heterotopic heart transplantation model that potentially could be used in future research projects. The purpose of this model was to provide adequate hemodynamic performance of the donor heart without disturbing the overall stability of homeostatic conditions. This model will be used to study xenotransplantation and transplant without immunosuppression.

**Progress**

The study was completed in September 2007. In this experiment the dog's anatomy was explored, the inferior vena cava and distal abdominal aorta were cannulated, and eventually the dog was placed on full cardiopulmonary bypass. In addition, catheters were successfully inserted in each chamber of the dog's heart with attachment to the transducers. This allowed simultaneous measurement and monitoring of hemodynamic variables. In the final step a dog's heart was transplanted, with attachments, to the inferior vena cava and distal abdominal aorta. The dog survived approximately 7 hours.

**16. Project title: Chlamydia Pneumoniae Deoxyribonucleic Acid (C. Pneumoniae DNA) & Coronary Artery Disease: A Pilot Study. RAC #: 2051061**

**Investigator/s:** Walid Hassan, Sahar Al Thawadi, Jalaluddin Bhuiyan, Nasser El Kum

**Project description**

This prospective, randomized pilot-study is primarily focusing on:

- a. the detection of *C. Pneumoniae* DNA in coronary sinus blood samples,
- b. the underlining correlation, if any, between *C. Pneumoniae* DNA and an increased risk of atherosclerosis, and
- c. determining the effects of *C. Pneumoniae* on levels of other cardiac markers such as c-reactive protein, B-type natriuretic peptide, Angiotensin II and Troponin T.

The results of this study may assist in better understanding the underlying inflammatory process associated with atherosclerosis and *C. Pneumoniae*.

**Progress**

Study enrollment has been completed and data is being analyzed.

**17. Project title: Long-term Outcome of Aortic Valve Replacement Using the Ross Procedure in KFHI. RAC #: 2051055**

**Investigator/s:** Zohair Al Halees, Bahaa Fadel, Maie Al Shahid, Mohammed Al Amri, Aly Al Sanei

**Project description**

This retrospective study is examining the Ross Procedure technique used to replace diseased or defective aortic valves with the patient's own healthy pulmonary valve, which in turn is replaced by a homograft. The study focuses on the long term follow-up of patients who had surgery from Jan 1990 to Dec 2004 for event free survival rate, re-operation(s) on the autograft and/or homograft, associated morbidities and mortality, and factors affecting long term survival of the valve replacement technique.

**Progress**

Four hundred sixty patients who meet the study criteria have been identified and data collection is ongoing.

**18. Project title: Permanent Pacing in Pediatric Patients: the King Faisal Specialist Hospital Experience. RAC #: 2051040**

**Investigator/s:** Majid Al Fayyadh, Abdullah Al Wadai, Waleed Al Manea

**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**

Three hundred forty-two pediatric patients have been enrolled in the Study and data has been analyzed. The mean follow up period is 5.2 years with the longest follow up of 19 years. The first pediatric PM implant was in 1985 and the last patient entered in 2005. The mean age is 2.4 years. The most frequent indications are: surgical AV block (57%), congenital AV block (21%) and sinus node dysfunction in (8%). The initial PM system was epicardial in 189 patients. After a mean follow up of 3.5 years (1 month-17 years), 70 patients had 116 revision procedures (lead malfunction 67, battery depletion 37, PM infection 8). Lead malfunction was encountered more with epicardial leads. There was no mortality directly related to the PM implantation procedure or function, however, there were 15 patients lost during the follow-up and 6 pts (3%) had non-pacemaker related death.

**19. Project title: Long-Term Outcome of Mitral Valve Repair Versus Mitral Valve Replacement Using Mechanical and Bioprosthetic Valves. RAC #: 2051016**

**Investigator/s:** Zohair Al Halees, Maie Al Shahid, Mohammed Al Amri, Aly Al Sanei, Bahaa Fadel

**Project description**

This retrospective review is studying the long-term effect of mitral valve repairs versus mitral valve replacement using mechanical and/or bioprosthetic valves. The aims of the study are to:

- a. compare the event-free survival periods associated with mitral valve repairs and replacement,
- b. describe the incidences of redo repairs and redo replacements,
- c. identify the factors contributing to the need for redo surgeries, and
- d. study the above factors on mortality and morbidity.

**Progress**

One thousand one hundred seventy patients were initially identified for this study; however preliminary data identified 779 only as meeting all study criteria. Data collection is ongoing.

**20. Project title: Percutaneous Ventricular Septal Defect (VSD) Closure: The KFSH&RC Experience. RAC #: 2041070**

**Investigator/s:** Mansour Al Joufan, Fadel Al Fadley, Ahmed AlOmrani, Saud Al Oufi, K Siddiqui, Zohair Al Halees

**Project description**

The aim of this retrospective review was to further examine the safety and effectiveness profiles of the Amplatzer® device used in VSD closing.

**Progress**

This study confirmed the high safety profile and effectiveness of the percutaneous membranous VSD closure and showed relatively lower incidence of rhythm disorder compared with the published international data.

**21. Project title: Does Modified Ultrafiltration Affect the Clinical Outcome Following Congenital Heart Surgery?. RAC #: 2041065**

**Investigator/s:** Ahmad Sallehuddin, Zohair Al Halees, Avedis Kaloghlian, Barima Afrane, Ahmed Jammali

**Project description**

This is a prospective, randomized, double-blinded study comparing conventional with modified ultrafiltration in patients undergoing cardiac surgery.

**Progress**

Data collection is ongoing.

**22. Project title: Incidence of Diastolic Heart Failure (DHF) in the Elderly. RAC #: 2041043**

**Investigator/s:** Fayez El Shaer, Walid Hassan, Mohamed Eid Fawzy, Suleiman Kharabsheh, Maie Al Shahid, Mahboob Nawaz, Nasser El Kum, Charles Canver

**Project description**

DHF with preserved systolic function is a unique and challenging disease. Several studies have shown age to be the most important factor in diastolic filling. This study will assess the prevalence, patient characteristics, morbidity and prognosis in elderly patients with DHF in comparison to systolic heart failure.

**Progress**

This study was completed in February 2007. Results showed (1) the prevalence of hypertension (86%) is a strong predictor of CHF in the elderly population, the second most common predictor of CHF was DM (46%), and the third common predictor was CAD (33%). Compared to SHF, DHF was more predominant in: elderly female (38 vs. 26%,  $P < .007$ ), hypertensive (86 vs. 72%,  $P < .0001$ ), with LV hypertrophy (67 vs. 24%,  $P < .0001$ ). Pulmonary systolic pressures, left atrial size, E/A ratio were lower in DHF as well as treatment with B-blockers, diuretics, ACEI, and digoxin. The length of hospital stay was similar in both groups ( $11.6 \pm 9.2$  in P group and  $11.8 \pm 10.2$  in R group). The readmission rate was higher in patients with reduced LV function [15.3% in group P and 37.1% in group R ( $p < 0.0001$ )]. The predictor for cardiovascular readmission was low ejection factor (EF). All cause morbidity was similar with 71.4% in-group P and 70.4% in R group. The total mortality was 6.74%, not statistically significant between both groups (17 patients 5.3% in group P and 18 patients in group R 9%) with a trend towards higher mortality in patients with reduced LV function. It was concluded that diastolic cardiac failure is a common and unique disease, more prevalent in elderly female hypertensive patients, has less rate of repeat hospitalization, and long-term prognosis is not better compared to SHF but still needs more effective management strategies.

**23. Project title: The Impact of the Right Ventricular To Pulmonary Artery Shunt on the Early Outcome of the Modified Norwood Procedure. RAC #: 2041041**

**Investigator/s:** Ahmed Bin Sallehuddin

**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**

Data has been collected and is currently being validated.

**24. Project title: Effect of Percutaneous Coronary Intervention (PCI) on Diabetic Patients. RAC #: 2031082**

**Investigator/s:** Walid Hassan, Adil Osman, Manzoor Memon, Fawaz Al Turki, Shabir Shah, Abdullah Kurnas

**Project description**

This retrospective study is analyzing the effect of PCI in diabetic patients with coronary artery disease. The analysis includes an assessment of the status of the coronary artery stents, the rate of re-stenosis, progression of or neo-atherosclerosis, and factors affecting regional wall motion and ejection fractions.

**Progress**

Six hundred eighty patients have been identified as meeting the study criteria. Data has been collected on approximately 50%.

**25. Project title: Is Myomectomy Justifiable in Preventing Recurrence of Discrete Subaortic Obstruction? RAC #: 2031072**

**Investigator/s:** Abid Awan, Ahmad Bin Sallehuddin, Zohair Al Halees, Mansour Al Joufan

**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 subaortic obstruction in patients with or without of myomectomy for discrete subaortic stenosis.

**Progress**

Data has been collected and is being cleaned and validated.

**26. Project title: Tetralogy of Fallot (TOF): A Retrospective Chart Review. RAC #: 2031061**

**Investigator/s:** Saud Al Oufi, Zohair Al Halees

**Project description**

A retrospective review of medical records of patients with TOF treated at the KFSH&RC. Patient progress is studied using data from clinical follow-up visits and echocardiography appointments.

**Progress**

Data collection on 958 patients has been completed and is currently being cleaned and validated.

**27. Project title: Establishing Atrioventricular Synchrony in Dogs with Surgically Created Complete Atrio-Ventricular (AV) Block. RAC #: 2031019**

**Investigator/s:** Majid Al Fayyadh, Waleed Al Manea, Ziad Bulbul, Mohammed Kandeel, Ghassan Siblini, Raafat El Sayed, Falah Al Mohanna

**Project description**

Using the dog as an animal model, this Project studied the possibility of creating an electrical AV connection in addition to, or as an alternative to, the AV node. Dogs were utilized and serial electrocardiograms were performed and studied for patterns of conductivity.

**Progress**

This study was completed in October 2007. Animals were operated on with and without growth factors. Two years after the procedure none of the dogs showed evidence of accessory pathway development which means one or more of the following is needed:

- longer follow-up
- procedure modification
- different growth factor formula/concentration or delivery method.

**28. Project title: Retrospective Medical Records Review of Truncus Arteriosus. RAC #: 2031015**

**Investigator/s:** Ahmed AlOmrani, Zohair Al Halees

**Project description**

The purpose of this retrospective Study is to analyze the data of neonates and infants who underwent primary repair of a truncus arteriosus anomaly at the KFSH&RC

from 1990 to 2000.

#### Progress

Sixty-six patients were identified as meeting the study criteria. Data has been collected and reviewed on 60.

#### **29. Project title: Fate of Bicuspid Neo-Aortic Valve in Arterial Switch Operation. RAC #: 2021058**

**Investigator/s:** Shahid Khan, Ahmad Bin Sallehuddin, Zohair Al-Halees, Ziad Bulbul

#### Project description

This project studied the long term integrity of the bicuspid pulmonary valve when used as an aortic valve in an arterial switch operation (ASO). Data from the medical records of patients who underwent ASO between 1986 and 2001 was collected and analyzed.

#### Progress

The results clearly showed that, in our experience, tricuspid valve in transposition of great arteries (TGA) is not a contra-indication to proceed with ASO.

#### **30. Project title: Outcomes of Contegra Grafts. RAC #: 2021049**

**Investigator/s:** Ahmad Bin Sallehuddin, Zohair Al-Halees, Ziad Bulbul

#### Project description

This retrospective review is examining the outcomes of patients who received the Contegra biological valve conduit as an alternative to homografts.

#### Progress

Sixty-three patients were enrolled in the study. Preliminary data showed: 13 were early mortalities (related to sepsis and vegetations), 2 were lost to follow up, 2 died late, and 17 underwent intervention (12 conduit replacements / 5 pulmonary artery stenting). Preliminary analysis of echocardiography showed that conduit regurgitation was not indicative of failure, while early conduit stenosis was. Sepsis was also associated with need for intervention. Freedom from intervention was 55% at 4 years. The use of supported conduits reduced the need for conduit replacement

#### **31. Project title: Optimal Approach of Atrioventricular Insufficiency in Fontan Patients. RAC #: 2021017**

**Investigator/s:** Ahmad Sallehuddin, Ziad Bulbul, Zohair Al Halees, Barima Afrane

#### Project description

This retrospective review was conducted to evaluate the outcome of patients less than 2 years of age who underwent a modified Fontan operation from 1986 to 2001.

#### Progress

This study was completed in October 2007. Data was reviewed on 340 consecutive Fontan patients from 1986-2001 records. Pre-Fontan demographic and hemodynamic data, operative details, operative mortality, late complication and survival data were compared.

Results showed that prior bidirectional cavopulmonary shunts in patients less than 2 years old improves the operative mortality following the Fontan operation and fenestrations shorten their length of stay. The Fontan procedure can be safely carried out in children younger than 2 years old with no significant differences in operative mortality, peri-operative recovery, long term complications and late survival.

#### **32. Project title: KFHI Surgery Registry. RAC #: 2001058**

**Investigator/s:** Zohair Al Halees, Aly Al-Sanei, Mohamed Eid Fawzy, Militiadis Stefadouros, Hani Sergani, Mohammed Al-Amri, Maie Al-Shahid

#### 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.

#### **33. Project title: Percutaneous Transluminal Coronary Angioplasty (PTCA) Registry. RAC #: 2001057**

**Investigator/s:** Hani Al Sergani, Jehad Al Buraiki, Bruce Dunn, Walid Hassan, Fawaz Al Turki

**Project description**

This is an on-going Registry of patients who underwent 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**

During the course of this progress period, the KFHI has:

- made a transition from utilizing bare metal stent to drug eluting stents,
- implemented new interventional devices including thrombectomy devices,
- adopted new techniques for percutaneous intervention in high risk patients including ostial and bifurcating lesions, and left main coronary artery stenosis. (All of the above resulted in an increase in the volume of patients going for interventional procedures instead of referring them for CABG.),
- recruited all myocardial infarction patients for primary angioplasty, given its documented superiority over thrombolytic therapy,
- examined outcomes of intracoronary IIb/IIIa agents for high risk complex lesions,
- made designed modifications necessary for the electronic formatting of data accumulation in Apollo, Lumedx Inc, CA, USA

**34. Project title: Valve Registry. RAC #: 2001055**

**Investigator/s:** Zohair Al Halees, Aly Al Sanei, Maie Al Shahid, Mohamed Eid Fawzy, Miltiadis Stefadouros, Hani Al Sergani, Mohammed Al Amri, Nasser El Kum

**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**

Data collection is ongoing.

**35. Project title: Mitral Balloon Valvotomy Registry Database. RAC #: 2001054**

**Investigator/s:** Mohamed Eid Fawzy

**Project description**

This registry includes short, intermediate and long-term follow-up data on patients who underwent a mitral balloon valvotomy procedure.

**Progress**

This registry has resulted in numerous publications in international journals.

**36. Project title: Pediatric Heart Catheterization Registry. RAC #: 2001053**

**Investigator/s:** Fadel Al Fadley, Ghassan Siblani, Ziad Bulbul, Mansour Al Joufan, Majid Al Fayyadh, Saud Al Oufi, Ahmad AlOmrani

**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.

**37. Project title: Congenital Heart Disease Registry. RAC #: 991026**

**Investigator/s:** Mansour Al Joufan, Zohair Al-Halees

**Project description**

This registry is a collaborative project between the KFHI and the Biostatistics, Epidemiology and Scientific Computing Department to collect data on pediatric patients with congenital heart disease.

**Progress**

This registry is ongoing.

**38. Project title: Clinical Trial of Glycar Quadrileaflet Mitral Valve (QMV) in Patients Requiring Mitral Valve Replacement. RAC #: 0971023**

**Investigator/s:** Zohair Al Halees, Aly Al Sanei, Maie Al Shahid, Mohammed Al Amri, Fadi Abdoun

### Project description

The aim of this multi-centre, prospective study is to evaluate the (QMV) for:

- a. feasibility of clinical insertion
- b. early mortality
- c. symptomatic benefit
- d. early valve related complications
- e. hemodynamic performance
- f. durability

### Progress

The investigators are collecting follow-up data only.

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# **LIVER TRANSPLANT & HEPATOBILIARY & PANCREATIC SURGERY**



The Department of

# LIVER TRANSPLANT & HEPATOBILIARY & PANCREATIC SURGERY

*T*he research activities in the Department of Liver Transplant are evolving, but not at the same pace as the progress of its infrastructure and clinical activities. All members are showing interest in research and are keenly establishing collaboration with other Department including the Research Center. Articles were published in the year 2007 in both local and international journals. Abstracts were accepted and presented in International Meetings. Research projects involve both Transplant Hepatology and Transplant Surgery in addition to Donor issues, with special emphasis on ideas that help the program development. However, research productivity can be improved once the problem of shortage of staff is solved and with the increase in the number of patients transplanted.

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*Director*  
**Mohammed Al Sebayel, MD**

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## RESEARCH ACTIVITIES

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### 1. Pan Arab Liver Transplantation Registry RAC No: 2071 022

**Investigators:** Hatem Khalaf, MD, Mohammed Al Sebayel, MD

#### Project description

Establishing a web-based Liver Transplantation registry aiming to monitor Liver Transplantation activities in KFSH&RC and towards the Arab World hoping for 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 identify the need of Liver Transplantation in KSA and the Arab World.
4. To document the treatment and assessment of treatment Outcome.

#### Progress and Major Findings

Since the approval of the registry by RAC in April 2007, the following tasks have been accomplished:

- **Registry Bylaws:** Dr. Hatem Khalaf has formulated the Registry Bylaws that will serve as guidelines for all participating liver transplant centers.
- **Phase I (Liver Transplant Patients at KFSH&RC):** This phase of the study has been entirely completed by entering the data of all liver transplant patients divided between 2 groups; the first group includes more than 160 patients who were transplanted in our institution by our local liver transplant program and the second group included 208 patients who were transplanted abroad and being followed up by the liver transplant program at KFSH&RC.
- **Phase II (Liver Transplant patients in Saudi Arabia):** Official invitations have been distributed along with the Registry Bylaws to the two major liver transplant centers in Saudi Arabia namely King Fahad National Guard Hospital and Riyadh Military Hospital asking their active participation. A positive response has been acquired from the RKH expressing to join the Registry.
- **Phase II (Liver Transplant patients in Arab World):** Official invitations have been distributed along with the Registry Bylaws to all liver transplant centers in the Arab World. Currently, a positive reply from Wady El-Nile Hospital in Cairo has been received. Four persons were invited to come and visit our Liver Transplant Program at KFSH&RC and at the same time to receive a formal training on how to use the web-based registry software. The visit was very successful and the visiting team has already started uploading their data into the registry software.

# **OBSTETRICS AND GYNECOLOGY**



The Department of

# OBSTETRICS AND GYNECOLOGY

The Department of Obstetrics and Gynecology is dedicated to the best patient care, teaching and research. At the end of 2007, the department had 18 RAC approved / ongoing projects. These projects included clinical, basic science, evidence based, prospective and retrospective case reports, either individually or in collaboration with colleagues, other departments and with national and international institutions.

*Chairman*  
Adnan Munkarah, MD, FACOG, FACS

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All divisions of OB/GYN have research proposals as follows:

- Gynecologic Oncology - 7
- Reproductive Medicine - 5
- Perinatology - 6

The objective of the department is to increase scientific knowledge of different obstetrics and gynecologic diseases including their epidemiology, risk and risk factors, prevention, diagnosis, treatment and prognosis.

It is the goal of the department to expand the basic and applied research by ensuring that each of the division will have at least three active research projects every year in collaboration with Research Centre and to be recognized in an international setting for high caliber researches.

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## RESEARCH PROJECTS

1. **A Multinational randomized phase III GCG intergroup study comparing Pegylated Liposomal Doxorubicin (CAELYX) and Carboplatin vs. Paclitaxel and Carboplatin in patients with epithelial ovarian cancer in late relapse (>6months). RAC #2051062**

**Investigator:** Adnan Munkarah, MD

### Project description

Ovarian cancer remains the leading cause of gynecologic cancer deaths. The majority of ovarian cancers (>90%) are epithelial in origin and often these cancers have already progressed to an advanced stage at the time of diagnosis. Today the standard therapy for patients with advanced ovarian carcinoma relapsing further than 6 months after previous platinum-based chemotherapy is paclitaxel and carboplatin. ICIN4/OVAR 2.2 trial has suggested that this doublet leads to better patient survival than the sole administration of carboplatin. Pegylated liposomal doxorubicin (Caelyx) is a new active drug that showed promising results in second line therapy for ovarian carcinoma. In particular patients with ovarian cancer in late relapse (> 6 months) included in a large randomized trial enjoyed a significantly superior survival when they were treated with Caelyx rather than with topotecan, the control arm. Given the fact that topotecan was previously demonstrated as effective as paclitaxel in the same population of patients, it can be assumed that Caelyx would be at least as effective as paclitaxel in patients with ovarian cancer in late relapse. The role of the Caelyx-carboplatin combination should be tested in this large randomized phase III trial evaluating if it might provide a benefit over standard paclitaxel-carboplatin chemotherapy.

### Progress

Completed. Final report submitted to ORA on December 8, 2007.

2. **Ovarian function preservation after laparoscopic ovarian transposition. RAC #2061026**

**Investigators:** Ismail Al Badawi, MD, Adnan Munkarah, MD, Jamal Al Subhi, MD, Hany Salem, MD, Ala Abduljabbar, MD, Balaraj, K.

### Project description

With progress in early detection of pelvic malignancy and better treatment outcome, the quality of life issues become an important target to aim when planning the treatment. Some pelvic malignancies affecting women in their reproductive years involve pelvic radiation therapy alone or combined with surgery, which leads to ovarian failure. In the past most of those women had managed their menopausal symptoms and osteoporosis with the conventional hormone replacement therapy (HRT). But since the Women's Health Initiative (WHI) study came out there was a major reluctance to use HRT. Laparoscopic ovarian transposition came as an alternative to preserve the ovarian function in pre-menopausal women with pelvic neoplasm requiring pelvic radiation therapy and avoiding the use of conventional HRT.

### Progress

Data collection, data entry and analysis on-going.

3. **A detailed study of patients and tumor characteristics of epithelial ovarian cancer in Saudi women. KACST and RAC #2051067**

**Investigators:** Adnan Munkarah, MD, Ismail Al Badawi, MD, Jamal Al Subhi, MD, Hany Salem, MD, Asma'a Tulbah, MD, Wafa Ajoor, MD

### Project description

Ovarian cancer continues to be one of the leading causes of cancer death in women around the world. According to the National Cancer Registry, it is the sixth most common cancer diagnosed in women in the Kingdom of Saudi Arabia. Patients are frequently diagnosed with advanced stage disease limiting the chances of cure. There is emerging data to suggest that ethnicity by itself may be an important prognostic factor. In fact, large population studies in the United States have shown that ovarian cancer patients of African descent suffer from a shorter survival than Caucasian patients, while women of Asian ancestry have better prognosis. While many factors can contribute to such a discrepancy, differences in the molecular phenotype of the tumors might be a significant reason. There is essentially no published study that has addressed the natural course and molecular changes associated with ovarian cancer in Arabic women in general or Saudi women in particular.

A descriptive study that reviews in detail the patients and tumor characteristics, treatment strategies as well as outcome and survival in ovarian cancer is urgently needed in the country. It will generate the necessary basic data and frame of work for developing future treatment and research strategies for ovarian cancer in Saudi and Arabic patients.

#### Progress

Data analysis on-going.

#### 4. Molecular signatures of diffuse large B-cell lymphoma (DLBCL), lung and ovarian cancer: a pilot study. RAC #2060008

**Investigators:** Kawla Al Kuraya, MD, Adnan Munkarah, MD, Jamal Al Subhi, MD, Ismail Al Badawi, MD, Hany Salem, MD, Asma'a Tulbah, MD

#### Project description

The clinical course of individual cancers is driven by the sum of molecular alterations in cancer cells. Accordingly, studies analyzing the expression of thousands of genes in tumors using cDNA and tissue microarrays have suggested a clinical relevance of the molecular signatures of cancers. However, limited information is available for many cancer types. Moreover, as increasing data suggest there are significant molecular differences between the same tumor types from patients of different ethnic backgrounds. It is unclear to what extent conclusions from foreign studies will apply to Saudi cancer patients. The proposal pilot project is intended to look for molecular signatures (or individual gene alterations) in diffuse large B-cell lymphoma (DLBCL), lung neoplasias and ovarian cancer based upon DNA alterations including loss of heterozygosity (LOH), gene amplification and expression analysis based upon tissue and cDNA microarrays. Qualitative evidence will be sought for differences in the molecular signature of the tumor types in Saudi and European patients. This study will provide the basis for future projects aimed at investigating the correlation of molecular profiles of tumor subtypes with clinical parameters such as response to treatment and survival. In addition, larger studies based upon data from this project will establish ethnic diversity in the molecular profiles of different tumor subtypes. The discovery of significant molecular differences between Saudi and Caucasians cancers would challenge the current practice of treating Saudi cancer patients according to Western protocols.

#### Progress

Data analysis on-going.

#### 5. Retrospective Analysis of Carboplatin/Paclitaxel combination in advanced or recurrent cervical cancer. RAC #2071055

**Investigators:** Adnan Munkarah, MD, Fatma Maraiki, PharmD, Mohammed Neimatallah, MD, Ismail Al Badawi, MD

#### Project description

Cervical cancer is the third most common malignancy and the second most frequent cause of death in relatively young women. Treatment of patients with advanced or recurrent disease focused only on palliation of symptoms and pain management. Cisplatin-containing regimen is the current standard of care for patients who are not candidates for either radiation or surgery. Multiple cisplatin-combination chemotherapy has been studied with relatively the same response rate around 40%. The toxicity remained the major concern with the combination regimen. Thus, carboplatin has been substituted as an alternative to cisplatin to minimize the toxicity profile. The carboplatin plus paclitaxel combination has been used for at least 5 years at King Faisal Cancer Institution. These data encouraged our institution to report our experience. The primary objective of this study is to assess progression free survival (PFS) and overall survival in ovarian cancer patients treated with carboplatin and paclitaxel. The secondary objective is to assess response rate to the chemotherapy combination.

#### Progress

Data collection and entry on-going.

#### 6. Clinical Proteomics: Development of Novel Biomarkers for Transitional Ovarian and Breast Cancer. RAC #2050011

**Investigators:** Hany Salem, MD, Abdulkareem Alaiya, MD, Jamal Al Subhi, MD, Ismail Al Badawi, MD, Adnan Munkarah, MD

#### Project description

Ovarian cancer is a major cause of morbidity and mortality in women in many parts of the world. Despite advances made in career treatment, the overall mortality

rates for most solid tumors including ovarian cancer remain unchanged. The mortality rate is similar across different countries, and approximately 60% of the women would die of the disease. Cancer proteomics is an aspect of biomedical research and will be an important contribution to our understanding of tumor biology. The aim of this project is to use proteomics approach to identify polypeptides that significantly differ in their concentrations between cells, tissue, serum and plasma, reflecting different stages of the disease and response to therapy. The study will provide the necessary data that is needed for further study or investigation for ovarian cancer and clinical proteomics of novel biomarkers for Saudi women.

#### Progress

Data collection on-going.

#### 7. Development of biomarkers for translational ovarian cancer research. RAC #2050043 (KACST 11-16)

**Investigators:** Hany Salem, MD, Abdulkareem Alaiya, MD, Jamal Al Subhi, MD, Ismail Al Badawi, MD, Adnan Munkarah, MD

#### Project description

Ovarian cancer is a major cause of morbidity and mortality in women in many parts of the world. Despite advances made in cancer treatment, the overall mortality rates for most solid tumors including ovarian cancer remain unchanged.

#### Progress

Data collection on-going.

#### 8. The Effect of Endometrial Thickness on Pregnancy Outcome in IVF-ET Cycles. RAC # 2061072

**Investigators:** Ahlam Al Ghamdi, MD, Khalid Awartani, MD, Saad Al Hassan, MD, Rafat Al Rejjal, MD, Serdar Coskun, Ph.D

#### Project description

After 30 years of *In Vitro* Fertilization (IVF), implantation rates are still around 10-20%. One of the factors is implantation of embryos to the endometrium. Endometrial thickness can be regarded as a reflection of the degree of endometrial proliferation in the absence

of intrauterine pathology, and it can be measured easily by ultrasonography. The purpose is to evaluate the relationship between endometrial thickness on day of human chorionic gonadotrophin administration (hCG) and pregnancy outcome in a large number of consecutive *in vitro* fertilization and embryo transfer (IVF-ET) cycles. A retrospective cohort study including all patients who had IVF-ET from January 2003-December 2005 conducted at a tertiary center.

#### Findings

A total of 2464 cycles were analysed. Pregnancy rate was 35.8% and increased linearly ( $r=0.864$ ) from 29.4% among patients with a lining of < 6 mm, to 44.4% among patients with a lining of > 17 mm. rate of change (ROC) showed that endometrial thickness is not a good predictor of pregnancy rate so a definite cut-off value could not be established (AUC=0.55). There is a positive linear relationship between the endometrial thickness measured on the day of hCG injection and pregnancy rate, and is independent of other variables. Hence aiming for a thicker endometrium should be considered.

#### Progress

Completed. Manuscript published in Journal of Assisted Reproduction and Genetics.

#### 9. Prevalence of hepatitis HCV & HBV in the population in the Kingdom of Saudi Arabia between years 2002 to 2005. RAC # 2061012

**Investigators:** Zainab Al Abdulla, MD, Mashael Al Deery, MD, Serdar Coskun, Ph.D., Khalid Awartani, MD

#### Project description

The American Society for Reproductive Medicine mandate the general screening for couples undergoing *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment for hepatitis B (HBV) and hepatitis C (HCV) to reduce the potential risk for transmission to an uninfected partner, and take the appropriate steps for gametes and embryos cryopreservation in the IVF laboratory. This study was concluded to see the prevalence of HCV and HBV in the IVF population. Retrospective cohort study, all couples undergoing IVF/ICSI treatment at King Faisal Specialist Hospital and Research Centre between January 2002 and May 2005 were screened for HCV and HBV. They were called seropositive when Anti HCV

is positive and confirmed with hepatitis C RIBA test. For hepatitis B, if HbsAG positive or anti-HBc positive test, the patient was labeled as HBV seropositive.

### Findings

HBV and HCV are highly prevalent in the IVF population, even more than the general population, all IVF programs are urged to screen these couples before starting treatment cycles and most importantly if gametes and embryos cryopreservation service are offered.

### Progress

Completed. Manuscript preparation.

#### **10. Gene expression profiling of granulose cells from patients undergoing infertility treatment. RAC #2050024**

**Investigators:** Serdar Coskun, Ph.D, Mehmet Inan, Ph.D, Saad Al Hassan, MD, Rafat Al Rejjal, MD, Khalid Awartani, MD, Laila Al Alwan, Pinar Ozand, MD

### Project description

Infertility is a worldwide problem affecting one out of 7 married couples. Tubal factor, endocrinological and anatomical abnormalities, endometriosis and polycystic ovaries could be considered as most common reasons in female infertility. Patients with infertility who could be treated with medical or surgical interventions are treated before they are referred to assisted reproductive techniques (ART, i.e. *in vitro* fertilization, intracytoplasmic injection, *in vitro* maturation). Currently, there are no markers to estimate the quality of the response or the outcome of the cycle in terms of pregnancies. Finding such markers will be great achievements to manage infertile patients. Recent developments in microarray technologies allowed scientists to investigate gene expression profiling in different biological models to better understand the molecular mechanism involved. Objective of this study is to look at the gene expression profiling of granulose cells from patients undergoing oocyte collection. After analysis, significantly differentially expressed genes will be identified and their significance will be further confirmed by real time real time-PCR experiments and quantification of corresponding proteins in follicular fluid.

### Progress

Data analysis on-going.

#### **11. Towards the understanding of sperm role in fertilization and early embryonic development: a pilot study. RAC #2040040**

**Investigators:** Serdar Coskun, PhD, Namik Kaya, PhD, Saad Al Hassan, MD

### Project description

Male factor infertility is common in patients undergoing infertility treatment in our hospital. Many of such cases have unexplained in nature and patients were treated without knowing the reason why they are infertile. A recent study has suggested that sperm delivers not only DNA but also RNA to the oocytes. Classical semen analysis consists of determination of sperm count, motility and morphology. These parameters although give idea about testicular function they are poor predictor of fertility potential of a male. A man could be infertile even semen analysis results are in the normal range. Many sperm function tests have been added to semen analysis to predict fertility potential of a man. However, most of such tests have been discontinued in clinical practical due to high false positive and negative results. In this pilot study, spermatozoa from a total of 100 patients will be screened for the levels of 6 mRNAs that have been pointed out to have role in fertilization and early embryonic development. Their levels will be correlated to the outcomes of the treatment. It is expected to find that some factors will be important in certain functions and they can be later used in male infertility diagnosis and/or treatment and to design further research for the understanding of male infertility.

### Progress

Data collection and analysis on-going.

#### **12. Isolated severe teratozoospermia: Is supraovulation and intrauterine insemination a reasonable option? RAC #2071062**

**Investigators:** Wajeih Al Aali, MD, Saad Al Hassan, MD, Serdar Coskun, Ph.D, Jana Shalaty, MD, Khalid Awartani, MD

### Project description

The choice of supraovulation and intrauterine insemination (SO/IUI) or IVF/ICSI as first line treatment for patients with isolated severe teratozoospermia has been controversial. Retrospective analysis of data at tertiary care governmental center where free treatment and medications are provided. Patients with isolated severe teratozoospermia (<4% normal morphology by strict Kruger's criteria with normal sperm count, motility, and normal (HSG) who was treated with SO/IUI during the period of 2000-2006 were identified from the unit database. The primary outcome was the life birth rate per patient starting the treatment. Secondary outcome was the patient's withdrawal rate from the program without completion of treatment as per unit protocol which is either having a live birth or completing four IVF treatment cycles.

### Findings

Patients with isolated severe teratozoospermia have low live birth rate per patient undergoing SO/IUI treatment, and reasonable live birth rate in IVF/ICSI. The prolongation of treatment in these patients with psychological and emotional stress led to high dropout rate even when the treatment is all funded. It is suggested that IVF/ICSI be the first treatment options for these patients.

### Progress

Data analysis on-going.

### 13. Five years experience in prenatal diagnosis in a tertiary care center in Saudi Arabia. RAC #2051042

**Investigators:** Nadia Al Hazmi, MD, Wesam I Kurdi, MD, Rubina Khan, MD, Alya Al Kaff, MD

### Project description

Prenatal diagnosis is frequently used to test for different genetic diseases, chromosomal abnormalities, and other ultrasound detected anomalies. There is no previous work done in our institution to evaluate such procedures. The aim of this study is to analyze the indications, results, and complication of various invasive tests in our population. This is a retrospective study at a tertiary care referral centre of all pregnancies that underwent invasive testing from 1 June 2001 to 30 June 2006. The indication of testing includes previous

history of abnormal pregnancies, previous child with a chromosomal anomaly, history of a genetic disease, parents with a balanced chromosomal abnormality and abnormal findings on ultrasound. Statistical analysis was performed using SPSS version 13.  $P > 0.05$  was considered statistically significant.

### Findings

It is concluded that perinatal diagnosis is an important tool for diagnosis of fetal disease. Screening tests are important but do not replace invasive testing. As we deal with large families and due to the high rate of consanguineous marriages, genetic diseases are important indication for prenatal testing in our population.

### Progress

Completed. Manuscript preparation.

### 14. Long term follow-up of patients with mitral valve balloon valvuloplasty during pregnancy. RAC #2071018

**Investigators:** Anjum Gulraze, MD, Wesam I Kurdi, MD, Mohammad Fawzi, MD

### Project description

To assess the long term (17 years) outcome of the mother and fetus after the Mitral Balloon Valvuloplasty (MBV) performed in pregnancy and its effects on future pregnancies of women. This is a retrospective study over a period of 17 years (1990-2004) of 27 pregnant women who underwent MBV by Inoue balloon catheter technique during second trimester. The long term (17 years) outcome of these mothers and their children will be assessed along with its effects on future obstetric carrier. Data will be collected by review of the medical records, telephone and direct communication with patients. Twenty seven (27) pregnant women between the ages of 17-46 years of age would be followed up for 17 + 3 years. The immediate success of MBV will be assessed by increase in mitral valve area and improvement in functional NYHA class. Its long term outcome would be analyzed for any re-stenosis/MVR. Obstetric outcome will be analyzed for incidence of abortions, mode of delivery (vaginal/cesarean), still births, pre-maturity and neonatal morbidity or mortality. Childhood development will be compared for their ages.

## Findings

MBV was successful in all patients who had significant improvement in NYHA class. This study demonstrates that Mitral Balloon Valvuloplasty is a safe and useful procedure during pregnancy. It had no short or long term adverse effects on the women's health and obstetric failure. The children born of such pregnancies had shown normal physical and mental development when compared to their siblings.

## Progress

Completed. Manuscript preparation.

### 15. Chromosomal abnormalities and pregnancy outcome in fetuses with increased nuchal translucency in Saudi population. RAC #2061074

**Investigators:** Wesam I Kurdi, MD, Maha Al Tuwajiri, MD

#### Project description

Despite the higher incidence of genetic disorders in Saudi Arabia which is thought to be related to high rate of consanguineous marriages, there is no study to our knowledge assessing the significance of increased nuchal translucency in Saudi population. The objective of this study are to evaluate the incidence, and the significance of increased nuchal translucency (NT) and the risk of chromosomal abnormalities in association with increased nuchal translucency in the population of King Faisal Specialist Hospital. This study is a retrospective chart and ultrasound films review of the pregnancies followed at Perinatology Clinics at KFSH&RC which is the premier tertiary care hospital in Saudi Arabia from 1997-2005. First trimester scan including measurement of the crown-rump length and NT (according to the criteria proposed by the Fetal Medicine Foundation in London) were done for all patients by a certified perinatologist who is certified by fetal medicine foundation. In pregnancies with increased NT, mothers were offered fetal chromosomal analysis and underwent follow up scans at 16 and 20 weeks of gestation. The majority of those mothers were delivered at our center. Their newborns were evaluated post-natal for any structural abnormalities, genetic disease or chromosomal abnormalities.

## Progress

Completed. Final report submitted to ORA on October 12, 2007.

### 16. Non-Immune fetal hydrops (NIHF): a challenge for prenatal diagnosis and management. RAC #2061058

**Investigators:** Majed Faden, MD, Wesam I Kurdi, MD, Maha Al Nemer, MD

#### Project description

Non-immune hydrops fetalis (NIHF) is a description of fetuses with sonographic demonstration of fluid collection in at least two different fetal compartments or single effusion combined with fetal anasarca. The reported incidence of NIHF is 1 in 1500 to 1 in 4000 deliveries. It is a non specific finding in a wide variety of fetal and maternal disorders, including hematological, genetic, chromosomal, cardiovascular, renal, pulmonary, gastrointestinal, hepatic, metabolic abnormalities, congenital infection and malformations of placenta or umbilical cord. Although many causes of fetal hydrops are responsive to therapy with reversal of hydrops and survival, the mortality of fetal hydrops generally remain high. Estimates of mortality vary between 60% and 90%. Prenatal diagnosis of some causes of NIHF is well established in chorionic villi and amniocytes. Awareness of diseases causing hydrops is useful as it gives an opportunity for risk evaluation, genetic counseling to parent and targeted prenatal diagnosis for at risk pregnancies. Our study is a retrospective review of all cases with NIHF maternal workup, fetal and neonatal outcome. The aim of this research is to evaluate the etiology, prognosis and outcome of fetuses with NIHF, our diagnostic workup and their yield.

## Progress

Data collection on-going.

### 17. The prevention of preterm delivery in women with cervical incompetence: a randomized controlled and observational trial with cerclage with and without cervical occlusion. RAC #2061010

**Investigators:** Wesam I Kurdi, MD, Maha Tulbah, MD

**Project description**

Preterm labor is the leading cause of perinatal morbidity and mortality. Strategies for reducing the incidence of preterm labor and delivery have focused on educating both physicians and patients about the risks for preterm labor and methods of detecting preterm cervical dilatation. The prevention of preterm delivery is a major desiderate in contemporary obstetrics. The research efforts have been punctuated by several ineffective intervention proposals. More recently, new areas of proposed preventive strategy have arisen, focusing on cervical competence. The purpose of this study is to determine if addition of cervical occlusion to routine prophylactic cervical cerclage is associated with a significant prolongation of pregnancy. The protocol is a large, simply designed, randomized-controlled, pragmatic multicentre trial, to confirm or refute the anticipated benefits of cervical occlusion vs. single cerclage. Additionally, the collaboration will give the opportunity to give a more detailed characterization of the group of women at repeated risk of preterm labor.

**Progress**

Data collection on-going.

**18. The 2-hour postprandial plasma glucose test: an evaluation of the accuracy of this screening test for gestational diabetes. RAC #2051043**

**Investigators:** Shahida Mushtaq, MD, Rubina Khan, MD, Maha Al Nemer, MD, Samia Mahgoub, MD, Wesam I Kurdi, MD

**Project description**

Gestational diabetes mellitus is a common medical complication and metabolic disorder in pregnancy occurring in 1-14% of patients depending on the population and criteria used for diagnosis. The objective of this study is to evaluate the accuracy of the 2-hour postprandial plasma glucose test as a screening test for gestational diabetes comparing the result of this screening test to the gold standard diagnostic test which is 75g OGTT. This is a prospective multicentric population based trial study which will include all women booked in KFSH&RC and Maternity and Children's Hofuf Hospital for antenatal care irrespective of maternal ethnicity or their risk.

**Progress**

Data collection on-going.

## PUBLICATIONS

### Gynecologic Oncology

- Pansare V, Munkarah AR, Schimp V, Nassar H, Saed G, Morris R, Ali-Fehmi R. Increased expression of Hypoxia-Inducible Factor 1 $\alpha$  in type I and type II endometrial carcinomas. *Mod Pathol*. 2007; 20(1):35-43.
- Munkarah AR, Chatterjee M, Tainsky MA. Update on ovarian cancer screening. *Curr Opin Obstet Gynecol* 2007; 19:22-26.
- Munkarah AR, Ali-Fehmi R, El-Hammady E, Malone JM, Saed GM. The effects of combining docetaxel and COX-2 inhibitors on proliferation and apoptosis in epithelial ovarian cancer. *Anti-Ca Drugs* 2007, 18(8).

### Perinatology

- Al-Dirbashi OY, Rashed MS, Al-Mokhadab MA, Al-Gahtani K, Al-Sayed MAA, Kurdi W. Stable isotope dilution analysis of N-acetylaspartic acid in urine by liquid chromatography electrospray ionization tandem mass spectrometry. *Biomed Chromatogr* 2007 (in press), published online in Wiley InterScience (www.interscience.wiley.com) DOI:10.1002/bmc.815.
- Al-Dirbashi OY, Rashed MS, Al-Gahtani K, Al-Mokhadab MA, Kurdi W, Al-Sayed MAA. Qualifications of N-acetylaspartic acid in urine by LC-MS/MS for the diagnosis of Canavan disease. *JIMD Short Report* #057 (2007) online, DOI:10.1007/s10545-007-0635-6.
- Kurdi W. Non-immune fetal hydrops: are we doing the appropriate test each time" *Journal of Prenatal Medicine*, 2007, 1(1):26-28.

### Reproductive Medicine

- Al Zayed M, Al Hassan S, Rashed M, Geba M, Coskun S. *Fertility & Sterility*, Vol 87, p.1468, 2007.

### Accepted for Publications

#### Reproductive Medicine

Al Ghamdi A, Coskun S, Al Hassan S, Al Rejjal R, Awartani K. The effect of endometrial thickness on the outcome of *in vitro* fertilization and embryo transfer

(IVF-ET). *Assisted Reproductive Journal*.

### Submitted for Publications

#### Perinatology

- Kurdi W, Al Tuwajri M. Chromosomal abnormalities and pregnancy outcome in fetuses with increased Nuchal translucency in a Saudi population. 2007.

#### Reproductive Medicine

- The effect of endometrial thickness on the outcome of *in vitro* fertilization and embryo transfer (IVF-ET). A Al Ghamdi, S Coskun, R Al Rejjal, S Al Hassan, K Awartani. Presented in the 14<sup>th</sup> World Congress on *In Vitro* Fertilization & 3<sup>rd</sup> World Congress on *In Vitro* Maturation, Montreal Canada, September 2007.

### Conference Proceedings

#### Perinatology

- Al Kaff A, Al Hazmi N, Al Ali W, Al Nemer M, Kurdi W. Five years experience in prenatal diagnosis in a tertiary care center in Saudi Arabia (abstract). *Ultrasound Obstet. Gynecol* 2007, 30:644.

#### Reproductive Medicine

- Human chorionic gonadotropin induced transcriptional profiling of granulosa cells from patients undergoing *in vitro* fertilization. S Coskun, MS Inan, LA Al Alwan, R Al Rejjal, K Awartani, S Al Hassan. Presented in American Society for Reproductive Medicine (ASRM) Conference, USA, 2007:11-13
- Isolated severe teratozoospermia, is super ovulation and intrauterine insemination on a reasonable option? W AlAli, S Al Hassan, S Coskun, J Shalaty, K Awartani. Presented in Middle East Fertility Society (MEFS) Conference, Turkey, 2007.
- The effect of endometrial thickness on the outcome of *in vitro* fertilization and embryo transfer (IVF-ET). A Al Ghamdi, S Coskun, R Al Rejjal, S Al Hassan, K Awartani. Presented in the 14<sup>th</sup> World Congress on *In Vitro* Fertilization & 3<sup>rd</sup> World Congress on *In Vitro* Maturation, Montreal Canada, September 2007.
- Transcriptional profiling of granulosa cells from patients with mature and immature oocytes retrieved. S Coskun, L AlAlwan, S Al Hassan, K Awartani, R Inan. Presented in MEFS, Turkey, 2007.

- Application of whole genome amplification and preimplantation genetic haplotyping (PGH) for single gene disorders. W. Qubbaj, K Awartani, S Al Hassan, A Abdulrahim, S Coskun. Presented in MEFS, Turkey, 2007.

#### Oral Presentations

- Can Empty Follicle Syndrome be Predicted? Madan S, Bukhari I, Al Hassan S, Rejjal R, Awartani K. 1<sup>st</sup> Annual Residents Research Day, KFSH&RC, January 2008.
- Effect of Weight Loss in Morbidly Obese Infertile Women on IVF. Al Sahan N, Coskun S, Al Hassan S, Awartani K. 1<sup>st</sup> Annual Residents Research Day, KFSH&RC, January 2008.
- Prevalence of Hepatitis B&C in the IVF Population in Saudi Arabia. Al Abdulla Z, Al Deery M, Al Hassan S, Coskun S, Awartani K. 1<sup>st</sup> Annual Residents Research Day, KFSH&RC, January 2008.
- Isolated Severe Teratozoospermia: Is Supraovulation and Intrauterine Insemination a Reasonable Option. Al Ali W, Al Hassan S, Coskun S, Shalaty J, Awartani K. 1<sup>st</sup> Annual Research Residents Day, KFSH&RC, January 2008.
- Public Awareness Regarding Need for Cervical Cancer Screening. Faden M. Salem H. 1<sup>st</sup> Annual Research Residents Day, KFSH&RC, January 2008.

# **MEDICAL GENETICS**



The Department of

# MEDICAL GENETICS

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*Interim Chairman*  
**Zuhair Rahbeeni, MD**

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## RESEARCH PROJECTS

### 1. Molecular genetic analysis of five inherited metabolic disorders frequently encountered in the metabolic clinic - (RAC # 2020011).

**Investigators:** Al-Sayed M (PI), AlAhmed S, Alsmadi O, Khalil H, Rashed M, Imtiaz F, Meyer B

#### Progress

#### Hydroxy-methyl-Glutaryl Co-A-Lyase (HMG) deficiency:

Apart from the common mutation that was reported in the previous report, two additional mutations were identified in the samples analyzed. One is a novel mutation (IVS6+1G>A) and the other has been reported previously. These mutations together account for over 90% of the abnormal alleles of HMG. This information will now enable us to perform large scale molecular testing for this disorder. The molecular assay for the common mutation is now established at ADL. This has allowed us to achieve the goals of the projects

#### Argininosuccinic aciduria (ASL):

Apart from the common mutation that was reported in the previous report, 5 additional mutations were identified in the samples analyzed. This accounts for over 90% of the abnormal alleles of ASL. This information will now enable us to perform large scale molecular testing for this disorder. The molecular assay for the common mutation is now established at ADL. Two abstracts and one publication were completed after approval from ORA. Couple of families with this disorder are enrolled now in the preimplantation diagnosis service, allowing us to achieve yet another important goal of the project

#### Propionic acidemia (PPA):

The common mutation G117D was found to account for 42% of the samples successfully tested. 5 additional (some novel) mutations are identified. Work is still going on to identify more mutations. As a result of the project, prenatal diagnosis and preimplantation diagnosis was made available for some families. The molecular assay for the common mutation is now established at ADL.

#### Methylmalonic Aciduria: (MMA):

There are three main genes involved in MMA-MMAA, MMAB and MUT. The first two have been screened and no mutation has been identified. MUT gene identified 2 common mutations so far.

Summary

Metabolic Disease	Gene	Locus	Mutation
Argininosuccinic Aciduria (ASA)	ASL	7q11.21	D115Y* G157R* R186W* G354X* G361X*
HMG-CoA Lyase (HMG)	HMGCL	1p36.11	R41Q IVS6+1G>A* F305fs(-2)
Propionic Acidemia	PCCA	13q32.3	G117D E126X* R129I*
	PCCB	3q22.3	C381Y* L388H* *K379R
VLCAD	ACADVL	17p13.1	S22X*
Methylmalonic Acidemia	MMAA	4q31.21	G37X R93H
	MMAB	12q24.11	
	MUT	6p12.3	

#### Publications

- Al-Sayed M, AlAhmed S, Alsmadi O, Khalil H, Rashed M, Imtiaz F, Meyer B "Identification of a common novel mutation in Saudi patients with Argininosuccinic Aciduria" *J. Inherit. Metab. Dis.* 2005; 28(6): 877-83.
- F. Imtiaz F, Al-Sayed M, AlAhmed S, Alsmadi O, Khalil H, Rashed MS, Meyer B "Novel Mutations Underlying Argininosuccinic Aciduria" *AJHG* (2005) Poster-1434
- Al-Sayed M, Imtiaz F, Alsmadi O, Rashed M, Meyer B "Mutations underlying 3-Hydroxy-3-Methylglutaryl CoA Lyase deficiency in the Saudi population" *BMC Med Genet.* 2006 Dec 16; 7:86.

### 2. Di George Syndrome: A Retrospective Study of 35 Cases From Saudi Arabia - (RAC# 2051 022).

**Investigators:** Zuhair Rahbeeni (PI), M. Anwar Iqbal, Zuhair Al-Hassnan, Fawzia Al-Sharief

#### Progress

Seventeen patients with DiGeorge syndrome (DS) were enrolled in the study. The age at diagnosis ranged from birth to 25 years. Family history was positive for 22q

deletion in one patient, 3 patients had family history of CHD and one had a sibling who died in infancy with unknown diagnosis, and another one had a sibling who died at 3 months of age with diagnosis of Wilson's disease. Clinical findings can be summarized as follows:

- Of the 17 cases with positive fluorescent in situ hybridization (FISH) for DGS, 8 cases had the cardinal features of DG, i.e. congenital heart disease (CHD), dysmorphic features and hypocalcemia.
- Of the 8 patients who had IgG analysis, 2 had ↓ IgG and 6 had normal IgG
- Heart lesions: Tetralogy of Fallot (55%), Coarctation of aorta and interrupted aortic arch (21.09%), VSD, ASD and PDA (30%), Peripheral pulmonary stenosis (8.3%), Truncus arteriosus (7.6%)

Our result confirmed the close association of conotruncal heart disorders and the diagnosis of DiGeorge syndrome. In terms of overall phenotype, we noted that most children who had CHD and dysmorphic anomalies had 22q11.2 deletion. We recommend the following strategy for DGS diagnosis in our patients: (1) A standard karyotype for all cases, (2) FISH test for detecting micro deletion 22q11.2.

A future goal of this study will be the screening of 22q11 deletion in patients with isolated defect of CHD or hypocalcemia or repeated infection. Our findings also indicate that some CHD is hardly associated with the deletion as zero cases associated with TGA.

#### Publications

- Zuhair Rahbeeni, Fawzia Al-Sharief, Zuhair Al-Hassnan, M. Anwar Iqbal. Di George Syndrome: A Retrospective Study of 35 Cases From Saudi Arabia [ in preparation]

#### 3. Role of the DFNB1 Locus in Hereditary Deafness within the Saudi Population – (RAC # 2040039).

**Investigators:** K. Taibah (PI), B. Meyer, M. Al-Owain, F. Imtiaz, Shelley J. Kennedy

#### Project description

Over 70% of hearing loss is non-syndromic, with the majority being autosomal recessive (AR) in nature. Mutations in the GJB2 (connexin 26) gene and GJB6 (connexin 30) gene are reported to cause greater than 50% of cases of AR non-syndromic hearing loss in North

America, with an estimated carrier frequency of 1 in 33. This study examined the frequency of mutations in these genes in individuals affected by non-syndromic AR hearing loss within the Saudi population. To date, less than 5% (3 of 135 patients) of affected Saudi individuals have been identified to have a mutation after complete sequencing of both GJB2 and GJB6. This finding was not wholly unexpected, as other hereditary diseases, such as cystic fibrosis, have unique genetic mutations within the Saudi population. Given that mutations in GJB2 and GJB6 have been excluded as the cause of non-syndromic AR hearing loss for the majority of Saudi families, we are now identifying families suitable for whole genome scanning to try and identify causative genes for hearing loss within this population. The findings of this study will be relevant to the newborn and premarital screening programs within the Kingdom.

#### Progress

- Blood has been collected and banked on 143 patients.
- The entire coding regions of GJB2 and GJB6 have been sequenced for 135 patients.
- 3 cases were identified to be homozygous for the common 35delG mutation in GJB2.
- No other mutations in GJB2 and GJB6 have been identified.
- As exclusion of a mutation in a gene with 100% confidence is not possible based on sequencing the coding region alone, we genotyped 3 closely linked microsatellite loci to GJB2 and GJB6 for each patient. The majority of our patients have consanguineous parents. Therefore, GJB2 and GJB6 can be excluded if heterozygosity is detected for these tightly linked markers.
- Genotyping for these three markers has been completed on 64 of 143 patients.

#### Future Research Direction

Results of this study to date have revealed that mutations in GJB2 and GJB6 are not the cause of the majority of non-syndromic AR hearing loss in the Kingdom of Saudi Arabia.

Blood samples are now being collected from a minimum of 6 family members in those families identified to have 3 or more affected individuals. These blood samples will be used to perform whole genome linkage analysis via 10K SNP Chip Affymetrix Genotyping. Results of this analysis may permit the identification of genes previously

identified in the literature to cause non-syndromic AR hearing loss or may lead to the identification of novel genes.

Identification of the genes causing non-syndromic AR hearing loss in the Kingdom of Saudi Arabia will permit accurate genetic counselling. At the family level, mutation identification in the causative genes will allow for the option of carrier testing for extended family members and future spouses. This will help identify couples at risk to have a child with hearing loss within families known to have non-syndromic AR hearing loss. Couples identified to be at 25% risk who do not wish to have a child with hearing loss will have the option of pursuing preimplantation genetic diagnosis. At the general population level, these results may have direct application to newborn and pre-marital screening programs.

#### 4. Genetic Mapping and Characterization of Nonsyndromic X-linked Mental Retardation in Saudi Families - (RAC # 2050 018).

**Investigators:** Zuhair Al-Hassnan (PI), Mohammed Faiyaz-UI-Haque (Co-PI), Nadia Sakati, Mohammed Al-Owain, Abdelghani Tbakhi, Mohammed Al-Dosari, Fawziah Al-Sharief, Eissa Faqieh

##### Project description

The main objective of this research project is to identify genes responsible for X-linked mental retardation in Saudi families. Scientific study is not available on this form of mental retardation in our population and genetic screening of population specific gene loci for MRX patients is not possible. Therefore, an etiological diagnosis cannot be made, leaving families without a practical genetic counselling or reproductive options. Detecting the causative mutations in affected families will serve several clinical purposes in such incurable disease. It will enable clinicians to confirm the diagnosis, apply preventive measures such as preimplantation genetic diagnosis, and screen at-risk family members for carrier status, and then targeted premarital screening could be implemented on individual families.

##### Progress

- We have enrolled two families with XLMR.
- We have carried a preliminary X chromosome screen using DNA from the first family. Following an X chromosome scan with the use of 48 microsatellite markers (ABI PRISM® linkage mapping set v2.5)

distributed along the X chromosome, we have successfully identified a recombination in four affected members between the proximal DXS8043 (Xq27.3) and the distal DXS8087 (Xq28) that corresponds to a physical distance of 8.7 Mb. Haplotype analysis was performed manually and a shared haplotype was identified in affected individuals.

- Molecular analysis on the second family is still in progress.

##### Future Research Direction

- To further refine the initial linkage region (~7.22 cM) for the first family.
- Analyze the linkage data on the second family.
- Extend the project by enrolling more families, collect their samples, and calculate their lod scores after devising the appropriate plan for each family.

##### Publications

- Zuhair Al-Hassnan, Halah Abalkhail, , Muhammad Faiyaz UI-Haque, Nadia Sakati, Mohammed Al-Owain, Abdelghani Tbakhi, Mohammed Al-Dosari, Fawziah AL-Sharief, Eisa Faqieh. Mapping Non-Syndromic X-Linked Mental Retardation in Saudi Population. 13<sup>th</sup> International Workshop on Fragile X and X-Linked Mental Retardation, Venezia Lido, Italy, October 3-6, 2007.
- Halah Abalkhail, Zuhair Al-Hassnan, Mohammed Faiyaz UI-Haque, Nadia Sakati, Mohammed Al-Owain, Abdelghani Tbakhi, Mohammed Al-Dosari, Fawziah AL-Sharief, Eisa Faqieh. Genetic Mapping and Characterisation of Non-Syndromic X-Linked Mental Retardation in a Saudi Family. The 57<sup>th</sup> Annual Meeting of the American Society of Human Genetics, San Diego, California, October 23-27, 2007.

#### 5. L-2-Hydroxyglutaric Aciduria: clinical, biochemical and molecular analysis in a large Saudi Family- (RAC # 2050013).

**Investigators:** Moeen Al-Sayed (PI), E. Faqieh (Co-PI), M UI Haque, A. Alduraihem, N.M. Saleh, H.A. Abalkhail, Mohammed Al-Owain

##### Progress

3 consanguineous families with L-2-Hydroxyglutaric aciduria are included so far. We studied 15 individuals and sequenced the entire coding regions and exon-intron boundaries which revealed two different homozygous

mutations in both families. In 1st family and 2nd family, we identified a novel single bp deletion "A1015" in exon 8, resulting in a frameshift in the translated protein and replacement of 12 novel amino acids before a premature termination. The mutation was found in a homozygous state in all 8 affected individuals. In the 3rd family, mutation analysis in 1 affected individual revealed a homozygous C1319A transition at codon 440, which changes Serine a hydrophilic acidically charged residue to Tyrosine a basically charged residue in a conserved low complexity region of gene. We also found that the two mutations are located in a highly conserved area across the multiple species which suggests that the substituted residues are important for protein folding and/or enzyme catalysis and may effect the pre-processing and folding mechanism of the protein inside the mitochondria

#### Publications

- M. Ul Haque, E. Faqieh, A. Alduraim, N.M. Saleh, H.A. Abalkhail, M. Al-Owain, A. Tbakhi, M. Al-Sayed "Novel mutations in two large Saudi families affected with L-2-Hydroxyglutaric aciduria" Poster at ASHG 56 Annual meeting, New-Orleans, USA, Oct 2006.

#### 6. Molecular Look on Early Infantile Primary Lactic Acidosis: Pilot Study (RAC# 2050009).

##### Project description

This study aims to understand the molecular basis of the onset and progression of the infantile primary lactic acidosis in the affected patients using microarray technology, mutation analysis and apoptosis specific assays. We will be analyzing the gene expression patterns and trying to determine the gene signatures specific to the onset and progression of this important disease at the early stages of the pathogenesis. Also, we will be utilizing the MitoLight Kit and DNA Fragment analysis to determine the beginning and advancement of the apoptosis in the patients. To be able to achieve our goals, we will be performing these experiments

periodically during the early stages of the disease onset and progression. Once the disease specific gene signatures are identified and stages of the apoptosis are clarified, we will characterize the significant genes of interest involved in this important disease. Furthermore, we will be doing mutation analysis for the mtDNA genes and nuclear genes known to involve in this disease.

**Investigators:** Mohammad Al-Owain (PI), Namik Kaya (Co-PI), Zuhair Rahbeeni, Pinar Ozand, Moeen Al-Sayed, Muhammad Faiyaz Al-Haque, Zuhair Al-Hassnan, Mehmet S. Inan, Saleh Al-Alaiyan, Khaled Abu-Amero, Ali Al-Odaib, Abdulghani Tbakhi

##### Progress

We have collected 5 cases (goal for 10 cases) of infantile primary lactic acidosis.

##### Future Research Direction

We have performed the gene expression studies on the 5 patients that have been recruited and is being analyzed. Meanwhile, we will continue to collect the required number of cases, an additional five cases. We have applied for an extension of the project for another year.

#### 7. Hereditary Tyrosinemia Type 1: Clinical, Biochemical and Molecular characterization with emphasis on response to NTBC- (RAC # 2050 022).

**Investigators:** Moeen Al-Sayed (PI), Faiqa Imtiaz (Co-PI), Mohamed Rashed, Zuhair Rahbeeni, Zuhair Al-Hassnan, Mohammad Al-Owain

##### Progress

22 subjects belonging to 7 families have been included in the study after obtaining informed consent. Blood has been obtained from all alive affected members, available siblings and parents. Seven mutations have been identified in HTT1 gene (V263M, D400H, IVS4+1G>A, G170V, P261L). Five are novel mutations.



**MEDICINE**



## The Department of

# MEDICINE

A Research Unit Working Group was established in 2007 and submitted a proposal to establish the Research Unit in Department of Medicine. A plan for research infrastructure including office space, personnel, i.e. full-time or part-time research nurse, research fellows, coordinator or assistant, and data entry operators. Research time allocation/protected time, approval and deadline of research proposals submitted for review, budget/resources, periodic reports, and rewards for projects that will be published in peer-reviewed journals. Establish data bank and tissue bank as well as local and national collaborations.

Complete the currently on-going projects. Establish new research projects on hot topics such as non-alcoholic steatohepatitis, liver cancer and Wilson's disease, hepatitis C virus infection: predictors of response, virologic response and resistance to adefovir therapy in patients with hepatitis B virus infection, stem cell transplant in end stage liver disease patients. Continue section research meeting once per month. Collaborate with Molecular Diagnostics, Research Centre, Hematology Department, and Radiology Department.

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*Chairman*

**Mohammad Alfadda, MD**

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## RAC-APPROVED RESEARCH ACTIVITIES

**Project title: Efficacy of combination therapy with PEG-Interferon  $\alpha$ -2a (Pegasys) plus Ribavirin in the treatment of Chronic Hepatitis C: A Retrospective Study. Approved on 18 September 2005 (RAC # 2051 035).**

**Investigators:** Hamad Al Ashgar, Khalid E Alsawat, Mohammed Q Khan, Naser Elkum, Saleim Dahab, Musthafa C Peedikayil, Abdullah Al Shehri, Abdullah Al Kalbani, Mohammad Al Fadda, Ingvar Kagevi, Mohammed Al Quaiz, Mohammad Rezeig, Khalid Al Kahtani

### Project description

This is the first large scale retrospective study in Saudi population, planned to assess the efficacy and safety of Pegasys (Peginterferon  $\alpha$ -2a ) and Ribavirin combination in the treatment of chronic hepatitis C at KFSH & RC, Riyadh.

### Aim of the study

The primary objective is to evaluate the response rate of combination therapy (Peginterferon  $\alpha$ -2a and Ribavirin) in chronic HCV, and secondary objective is to analyze the effect of HCV genotype, HCV RNA Level (quantitative), and histological staging on the success of viral eradication.

### Patients & Methods

Clinical, biochemical, and virological parameters were collected at time 0 (pre-treatment), and at 12, 24, 48 & 72 weeks post-treatment. The mean $\pm$ SD age was 49.1 $\pm$ 13.0 years; 229(68.4%) were males, mean $\pm$ SD body mass index was 27.8 $\pm$ 7.4, 85(25.4%) were diabetic, 25(7.5%) had renal impairment, 136(40.6%) previously received interferon  $\pm$  ribavirin therapy, and 247(73.7%) underwent pre-treatment liver biopsy. Patients with genotype 1, 2 or 3, 4, and mixed genotype were 60(22.15%), 30(11.0%), 148(54.4%), and 34(12.5%) respectively.

### Main results

Early viral response ( $\geq 2$ -log<sub>10</sub> HCV-RNA decline 12-weeks post-treatment) was achieved in 253(75.3%). Patients who completed 48 weeks treatment were 292(87.1%), of them 121 (75.6%) achieved ETVR,

161(55.1%) continued to have SVR, and 60(20.5%) had viral relapse following end-of-treatment response, that is 48.1% and 17.9% of all patients (n=335) respectively. Non-responders (NR) were 71(24.3%) patients and 43(12.8%) were unable to complete treatment (due to side effects or lost follow-up). Compared to relapsers, patients with SVR were significantly younger (p=0.000), non-diabetics (p=0.015), had higher serum albumin (p=0.007), had less pre-treatment inflammatory grade (p=0.011), infected with genotype 2 or 3 (p=0.014), and treatment-naive patients (p=0.001). However, in stepwise multivariate logistic regression analysis, only being treatment-naive and low pre-treatment inflammatory score were the independent predictors of SVR (p=0.005 and p=0.018, respectively).

### Conclusions

Combination therapy, if tolerated and completed, is effective in treating chronic HCV patients, especially those with no previous interferon therapy, and lower pre-treatment inflammatory grade.

### Progress

This project was closed, and presented in local, national, and international scientific meetings in 2007. Two papers came out of it. One accepted in the *Saudi Journal of Gastroenterology* (in press), and the other is submitted to the *World Journal of Gastroenterology*, and the decision is awaited.

**Project title: Efficacy of Peginterferon  $\alpha$ -2a, in HbeAg-Negative Chronic Hepatitis B: Naïve Versus Lamivudine Resistance Patients. Approved on 21 August 2007 (RAC #2051 015).**

**Investigators:** Al Ashgar H, Khan MQ, Elkum N, Imambaccus H, Al Mohaizaie A, Al Suhaibani H, Al Omari M.

### Project description

To study pegasys in cases of chronic HBV precore mutant.

### Progress

A multi center study is in progress and has endorsed 39 patients for the last year.

**Project title: Intra-gastric Balloon in Obese Patients; KFSH&RC Experience. Approved on 11 October 2006 (RAC # 2051 038).**

**Investigators:** K Kahtani, M Q Khan, N Elkum, H Al Ashgar, B Fahad, M S Al Sofayan, S Abdulrahman, S Dahab

#### Project description

To evaluate the effectiveness, tolerance, and safety of a bio-enteric intra-gastric balloon (BIB) for the treatment of obesity as adjunct to diet, physical training, and behavioral modifications in Saudi patient who failed to respond to diet and physical activity alone.

#### Background

Bio-enteric intra-gastric balloon (BIB) insertion is gaining popularity for weight reduction in obese patients. We evaluated the efficacy, tolerability, and safety of BIB in the treatment of obesity.

#### Patients & Methods

A total of 173 Saudi obese patients (mean±SD age 34.5±11.6 years, 58(33.5%) were males) underwent BIB (InaMed Corporation, CA, USA) insertion were followed up clinically, biochemically, and endoscopically for 6-12-month. The mean±SD baseline body weight, excess weight, and body mass index (BMI) were 123.5±39.6 kg, 68.9±40.0 Kg, and 46.7±14.1 kg/m<sup>2</sup> respectively. Associated dietary control, exercise, and medical treatment were used in 67(38.7%), 60(34.7%), and 3(1.7%) respectively.

#### Main Results

BIBs were safely and successfully inserted in 15.1±6.2 minutes, filled with 626.2±41.7 mL methylene-blue solution, removed after a period of 189.7±68.3 days, within 14.1±6.3 minutes. BIB was not tolerated for 6 months in 33(19.8%) patients. Body weight and BMI at 6 & 12 months post-insertion were significantly reduced to 112.5±35.7 kg and 43.1±13.1 kg/m<sup>2</sup> & 110.7±34.5 Kg and 42.3±12.6 kg/m<sup>2</sup> respectively (p<0.01 versus baseline by one-way ANOVA). Also, the mean absolute weight loss and mean % excess weight reduction (EWR) at 6 & 12 months post-BIB insertion were 13.5±13.5 kg and 19.5±21.8 & 14±18.5 kg and 18.0±25.8 respectively. No mortality or major complications has occurred. EWR of ≥25% occurred

in 24.1% and 30.1% of patients at 6 and 12 months post-insertion respectively.

#### Conclusion

BIB is a safe, simple, and potentially efficient procedure that is well-tolerated by the majority of patients.

#### Progress

The retrospective study of intra-gastric balloon in obese patients experience in KFSH&RC is done. Data on 173 patients who received intra-gastric balloon, their data has been expected and tabulated in the data sheet and the final results were presented in both local and national meetings in 2007. The full results were accepted for publication in *Obesity Surgery* (In press).

**Project title: A Retrospective Analysis of Inflammatory Bowel Disease at a Tertiary Center in Saudi Arabia. Approved on 03 June 2007 (RAC# 2071 014).**

**Investigators:** Al Fadda M, Al Kahtani K, Al Ashgar H, Kagevi I, Al Quaiz M, Rezeig M, Peedikayil MC, Khan MQ, Helmy A

#### Progress

After the approval was obtained, the medical record numbers of inflammatory bowel disease patients treated in KFSH&RC were collected. A total of 379 patients were identified. Data collection was initiated and is still ongoing.

**Project title: A Retrospective Analysis of Value, Appropriateness and Yield of Colonoscopy in a Tertiary Center in Saudi Arabia. Approved on 29 May 2007 (RAC#2071 020).**

**Investigators:** Alfadda M, Al Kahtani K, Al Ashgar H, Rezeig M, Al Quaiz M, Kagevi I, Khan MQ, Peedikayil MC, Alshehri A, Helmy A

#### Progress

Data were collected, analyzed, and an abstract from the initial data of 6 months was presented in a local meeting in 2007 (see below). A total of 976 cases were collected in 3 years. We are currently doing the final analysis to be followed by submitting the full article for publication.

## Introduction & Aims

Colonoscopy plays an increasingly important role tool, and is considered a gold standard for screening, diagnosis, surveillance, and treatment of colorectal diseases. As part of an ongoing project: "A retrospective analysis of value, appropriateness, and yield of colonoscopy in a tertiary center in Saudi Arabia", we present the initial analysis of the colonoscopic reports from 1 January 06 until 27 June 2006 (a period of 6 months).

## Methods

All colonoscopy reports were retrieved and data related to the procedure, sedation, preparation, interventions and findings were collected in a pre-made data collection form, and then taken to SPSS data sheet for analysis. The number of colonoscopy procedures done was 334. The Mean  $\pm$  SD age of patients was 51.2  $\pm$  15.6 years with a male/female ratio 174(52.1%)/160(47.9%).

## Results

Sedation was reported in 206 (91.6%), and included pethidine, midazolam, fentanyl, and others in 4%, 2.5%, 84.7%, 44.3%, and 7.2% respectively. Preparation was good, satisfactory, and poor in 54.2%, 32.6%, and 12.0% respectively. Indications were variable and included abdominal pain in 15%, bloody diarrhea in 1.5%, bleeding per rectum in 14.4%, constipation in 3.6%, diarrhea in 4.5%, obstruction in 1.5%, mass in 0.66%, weight loss in 1.2%, follow up in 29%, surveillance in 6%, due to radiological finding in 3%, primary gastrointestinal cancer in 6.3%, anemia in 8.7%, and others in 7.8%. Extent of examination was till the terminal ileum, caecum, hepatic flexure, transverse colon, and others in 80(24%), 216(64.7%), 7(2.1%), 9(2.7%), and 22(6.6%) patients respectively. Colonoscopic finding were detected in only 206 (61.7%) patients and was normal in the remaining 38.3%. Findings were mainly ulcerative colitis in 17.4%, polyposis in 21.3%, hemorrhoids in 18.9%, malignancy in 5.7%, diverticulosis in 12.3%, and others in 12%. Colitis was detected in 58 patients and was mild, moderate, and severe in 26(44.8%), 23(39.7%), and 9(15.5%) respectively. It was pan colitis in 31(47.8%) patients. Tumours were mainly in rectosigmoid area, descending colon, transverse colon, and right side of the colon in 8(42.1%), 1(5.3%), 1(5.3%), and 9(47.4%) respectively. Biopsies and polypectomies were the main intervention, being done in 148(44.6%) and 36(10.8%) patients respectively.

## Conclusion

Although this data represent initial analysis of an ongoing project, it reflects the current practice and characteristics of patients in a tertiary center. Colonoscopy remains to be beneficial in diagnosing and screening of colorectal diseases, its appropriateness need to be reevaluated especially in patients who are less likely to have pathological abnormalities.

**Project title: A 10-Year Retrospective Analysis of Different Therapeutic Modalities in Chronic Hepatitis B Virus Infection in a Tertiary Center in Saudi Arabia. Approved on 30 June 2007 (RAC#2071 030 ).**

**Investigators:** Al Ashgar HI, Al Kalbani A, Al Kahtani K, Alfadda M, Rezeig M, Al Quaiz M, Kagevi I, Al Mana H, Khan MQ, Peedikayil MC, Alshehri A, Helmy A, Al Fadda A

## Progress

After the approval was obtained, the medical record numbers of chronic hepatitis B patients treated in KFSH&RC were collected. A total of 400 patients were identified. Data collection was initiated and still going on, data from 100 records are already collected .

**Project title: A Multicenter, Open-label, Randomized Comparative Study of Tigecyclinevs.Ceftriaxone Sodium Plus Metronidazole for the Treatment of Hospitalized Patients with Complicated Intra-abdominal Infection. [Protocol 3074A1-315-WW] – Approved on 26 March 2007 (RAC# 2061 076).**

**Investigators:** Dr Abdullah Al Hokail, Consultant, Infectious Diseases, Department of Medicine; Dr Naser Al Sanea, Consultant, Section of Colorectal Surgery, Department of Surgery; and Dr Sahar Al Thawadi, Section Head, Microbiology, Department of Pathology & Laboratory Medicine

## Project description, Progress, Major Findings

A multicenter, open-label, randomized study comparing efficacy and safety of Tigecycline vs. Ceftriaxone and metronidazole in complicated intra-abdominal infections. KFSH&RC is one of the 50 centers around the world participating in this study and the only center in the region. We are expected to enroll 6 patients but so far only 1 patient has been enrolled and based on this we do not have any findings so far.

**Project title: Proposal for Clinical Evaluation and Genetic Study of a Saudi Family with familial Primary Cortisol Resistance. Approved on 07 July 2007 (RAC# 2070 003).**

**Investigators:** Dr Hussein Raef, Dr Yufei Shi, Minjing Zou, and Essa Al-Beitie

#### **Project description, Progress, Major Findings**

The study was initiated after diagnosis of primary cortisol resistance (first reported case in the region) in a young man with severe uncontrolled hypertension. The clinical and biochemical profiles of all family members were studied and revealed severe cortisol resistance in 2 siblings. Other members were asymptomatic but nevertheless there was a subclinical biochemical cortisol resistance in 2 members.

The genetic analysis of the Glucocorticoid Receptors (GR2) gene revealed very interesting findings: Homozygous mutation G679 was found in all clinically affected members (first reported in the world literature), where as heterozygous mutation was found in all other members. A new and potentially important finding was a polymorphism that was only seen in members with normal cortisol response to dexamethasone and not in those with subclinical cortisol resistance indicating possible interaction between the polymorphism and the heterozygous mutation.

The findings described above represent:

- The first case of this rare disease described in the whole region.
- The sixth family with this disorder reported worldwide
- The first homozygous mutation at G679 were reported.

- The most severe cases of clinical cortisol resistance ever reported, requiring innovative methods of treatment never described before.
- The discovery of the 3 affected cases provided opportunity for them for adequate treatment at KFHS&RC including one member with progressive renal failure which is listed for renal transplant.
- The following abstracts/publication have resulted so far from this study.

#### **Abstract**

Hussein Raef, Essa Baitei, Minjing Zou, and Yufei Shi. Familial primary cortisol resistance in a Saudi family, due to homozygous mutation (G679S) of the Ligand binding domain (LBD) of the glucocorticoid receptor (GR- $\alpha$ ) gene. Department of Medicine's 9<sup>th</sup> Annual Research Celebration Day, 29 May 2007.

#### **Abstract**

Hussein Raef, Essa Y Baitei, Minjing Zou and Yufei Shi. Familial primary cortisol resistance in a large family, due to homozygous mutation (G679S) of the ligand binding domain (LBD) of the Glucocorticoid receptor gene. The Endocrine Society's 89<sup>th</sup> Annual Meeting. Toronto, Canada. 02-05 June 2007.

#### **Publication**

Hussein Raef, Essa Y Baitei, Minjing Zou and Yufei Shi. Genotype-phenotype correlation in a family with primary cortisol resistance: possible modulating effect of the ER22/23EK polymorphism. *European Journal of Endocrinology* 158 577-582.

The findings of our study could also present an opportunity of collaboration with world authorities on cortisol resistance like Steven Lambert and John Koper at Erasmus Medical Center in the Netherlands who had showed interest in our findings.



# **PATHOLOGY AND LABORATORY MEDICINE**



The Department of

**PATHOLOGY AND LABORATORY  
MEDICINE**

*Chairman*  
Fouad Al-Dayel, MD

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## ONGOING RESEARCH PROJECTS

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### Assisted Reproductive Technology Section

#### 1. RAC# 2071076: KFSH experience with preimplantation genetic diagnosis (PGD) retrospective analysis

**Investigators:** Qubbaj, W., Awartani, K., Al-Rejjal, R., Al-Hassan, S., Al-Deery M., Al-Duraim, A., Coskun, S.

This study is recently approved and in progress. The aim of the study is to investigate the results obtained from PGD cycles. This project will allow us to counsel our patients and report our experience to the medical community.

#### 2. RAC# 2021023: Pre-implantation genetic diagnosis for the most prevalent metabolic disorders in Saudi Arabia

**Investigators:** Odaib A, Aqeel A, Jaroudi K, Sakati N, Ozand P, Coskun S.

This project is in collaboration with Research Center Genetic Department and sponsored by PSCDR. This project involves in identifying mutations and performing PGD in 5 most common metabolic disease including Niemann-Pick, Canavan, Propionic Aciduria, Gauchers and Phenylketonuria. Several novel mutations are identified in Canavan, Propionic Aciduria and Gaucher disease. Several successful PGD cycles were performed and normal babies born in Phenylketonuria and Niemann-Pick diseases. Niemann-Pick PGD was the first in the literature and has been published in Prenatal Diagnosis. The publication for reporting novel mutation is under progress.

#### 3. RAC# 2061072: The effect of endometrial thickness on pregnancy outcome in IVF-ET cycles

**Investigators:** Al-Ghamdi A, Coskun S, Al-Hassan S, Al-Rejjal R, Awartani K.

This is a collaborative project between Departments Obstetrics and Gynecology, and Pathology and Laboratory Medicine. It aims to investigate the effect of endometrial thickness on IVF cycle outcome. There was a positive correlation between endometrial thickness and the establishment of pregnancy. A manuscript is under preparation to report the results.

#### 4. RAC# 2040040: Towards the understanding of sperm role in fertilization and early embryonic development: a pilot study

**Investigators:** Kaya N, Al-Mayman H, Al-Hassan S, Coskun S.

This project is in collaboration with Research Center Genetic Department and Flow Cytometry core facility. The aim is to analyze the presence and quantification of clusterin, AKAP4, protamine-2, HSBP1, FOXG1B and WNT5A mRNA in the sperm of patients undergoing infertility treatment and correlate their amount to the fertilization and cleavage rates, and early embryonic quality including embryonic arrest and acellular fragmentation rates. The sample collection and laboratory analysis have been completed, and data analysis under progress.

#### 5. RAC# 2061012: Prevalence of HCV and HBV in the population in the KSA between year 2000-2005

**Investigators:** Al-Abdulla Z, Al-Deery M, Al-Hassan S, Coskun S, Awartani K.

This is a collaborative project between Departments Obstetrics and Gynecology, and Pathology and Laboratory Medicine. The study was conducted to investigate prevalence of HCV and HBV in patients undergoing IVF. The results showed a high prevalence and it warrants screening of all patients before starting a cycle to prevent freezing of embryos for future cycles.

#### 6. RAC# 2050024: Gene expression profiling granulosa cells from patients undergoing infertility treatment

**Investigators:** Coskun S, Inan M, Al-Hassan S, Al-Rejjal R, Awartani K, Al-Alwan L, Ozand P.

This project is in collaboration with Research Center Genetic Department. The aim is to investigate the gene expression profiling of granulosa cells from patients undergoing oocyte collection. The responses were analyzed according to hCG dose and presence of immature follicles. The hCG induces enormous changes in the gene expression of granulosa cells. Transcriptional profiling of granulosa cells is different in patients with germinal vesicle (GV) oocytes compared to the one without immature eggs. It seems that events that lead to hypoxia and vascularization of ovarian follicles could be implicated in obtaining immature eggs. These observations could help us in understanding the mechanisms of hCG action

and finding the pathways possibly involved in healthy follicular maturation. The results were presented in American Society of Reproductive Medicine and Middle East Fertility Society meetings. Manuscripts are under preparation.

**7. RAC# 2071062: Isolated severe teratozoospermia: is superovulation and intrauterine insemination a reasonable option?**

**Investigators:** AlAali W, Al-Hassan S, Coskun S, Shalaty J, Awartani K.

This is a collaborative project between Departments Obstetrics and Gynecology, and Pathology and Laboratory Medicine. The cycle outcomes of intrauterine insemination treatment were compared to *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment in patients with isolated severe teratozoospermia. The results showed that IVF/ICSI should be the first line of treatment in this group of patients.

**Hematology Section**

**1. RAC# 2001007: Flow Cytometric Analysis in Childhood Acute Lymphoblastic Leukemia in KSA: A Prospective Study of Expression and Correlation with Outcome**

**Investigators:** Owaidah, T.

Acute Lymphoblastic Leukemia (ALL) is common childhood leukemia and KFSH&RC is considered to be one of the world leaders for the treatment of childhood Acute Lymphoblastic Leukemia. In this study we are looking for an antigen expression and correlate with outcome in the purpose of finding specific phenotypic expression that is associated with outcome.

**2. RAC# 2001045: Registry of Thromboembolic Disorders**

**Investigators:** Owaidah, T.

This is an ongoing registry initiated by the Section of Internal Medicine, to look at the various of Thromboembolic risk factors. The purpose is to study local presentation, incidence, and prevalence of these risk factors.

**3. RAC# 2030018 Molecular Genotyping of Hemophilia A among Saudi Patients**

**Investigators:** Owaidah, T.

Hemophilia A is a rare but serious disease that has great implication on families with increase in the management cost. The purpose of this study is to identify the molecular genotype in Saudi population for carrier detection and prevention.

**4. RAC# 2031027 Acute Promyelocytic Leukemia Treatment Protocol-II**

**Investigators:** Owaidah, T.

This study is adopting a new protocol for the treatment of Acute Promyelocytic Leukemia as a new model in the purpose to improve the outcome and decrease the toxicity.

**5. RAC# 2041040 Hemophilia and Von Willebrand Disease Registry**

**Investigators:** Owaidah, T.

Bleeding disorders are common haematological disorder. However, the prevalence and clinical presentation is not well-studied in the Kingdom of Saudi Arabia. The purpose of this registry is to identify the incidence, prevalence of these haematological disorders among Saudi population.

**6. RAC# 2041049 Retrospective Review of HIV Infection in Hemophiliacs**

**Investigators:** Owaidah, T.

Hemophilia is a rare but serious disorder with many complications that can arise from the disease and subsequent treatment. These patients are at high risk of transmission of various viruses due to frequent transfusion of blood products. HIV is one of the serious infections this patient is prone to have.

**7. RAC# 2050040: Chronic Myeloid Leukemia: Development and Validation of Therapeutic Hematoproteomic Biomarkers**

**Investigators:** Owaidah, T.

Chronic Myeloid Leukemia (CML) is a common disorder with known molecular genetic pathology. Recently the introduction of targeted therapy had made remarkable

change in the nature of the disease. In this study were looking at the different Hematoproteomic Biomarkers for possible use as a target therapy.

**8. RAC# 2060021: Proteomics Approach to Biomarker Discovery in Aplastic Anemia.**

**Investigators:** Owaidah, T.

Bone Marrow failure syndromes represent a group of patients that require bone marrow transplantation as a curative modality with its treatment related mortality and morbidity. In this study we are exploring various proteomics approach for possible development of new biomarkers that can be targeted for the treatment of Aplastic Anemia.

**9. RAC# 2061056: Evaluating the Knowledge, Attitudes and the Psychosocial Impact of Premarital Screening for Hemoglobinopathy in the Saudi Population**

**Investigators:** Owaidah, T.

Genetic screening is an important root to control and minimize transmission of genetic disorders. Saudi Arabia started the 1st national premarital screening program in 1424 to control inherited hemoglobin disorders. In this study we are evaluating the knowledge, attitudes and the psychosocial impact of this program.

**10. RAC# 2070002: Monitoring of Acute Myeloid Leukemia Using a Serum Tumor Marker and Evaluation Post Cryopreservation**

**Investigators:** Owaidah, T., Al-Sayed, H.

Acute Myeloid Leukemia (AML) is a common adult cancer. The diagnosis of AML is enhanced by immunophenotyping, one of the specific markers for the diagnosis for CD117. In this study we are looking for a soluble form of CD117 as a tumor marker.

**11. RAC# 2070014: Clinical, Histopathological, Biochemical and Molecular Characteristics of Neuronal Ceroid Lipofuscinosis in Saudi Arabia**

**Investigators:** Owaidah, T.

Neuronal Ceroid Lipofuscinosis is a rare disease

where different clinical presentation and different histopathological, biochemical and molecular characteristics of Neuronal Ceroid. In this study, we are looking respectively at these patients in Saudi Arabia population.

**12. RAC# 2081029: Effectiveness of the Real ART Malaria LC Real-time PCR Assay in Blood Bank Donors for Malaria Detection**

**Investigators:** Owaidah, T.

Malaria is an endemic disease in Saudi Arabia. Malaria can be transmitted through blood component and few cases were reported from Saudi Arabia. The gold standard test for screening and diagnosis of malaria infection is by Giemsa stained blood film. This test is laborious and very subjective. For this reason, we are evaluating the molecular real-time malaria test for possible use in Blood Bank donor screening.

**13. RAC# 2081031: Evaluation of a New D-Dimer Test in Combination with Pretest Clinical Probability Score for Diagnosis of Pulmonary Embolism and Deep Venous Thrombosis**

**Investigators:** Dr. Tarek Owaidah

Deep venous thrombosis and pulmonary embolism are common disorders that requires extensive and costly diagnostic imaging techniques. D-Dimer recently a significant tools that helps clinical decision about thrombosis. In this study, validating a new quantitative D-Dimer test and measures the positive predictive values using D-Dimer and pretest clinical probability score system in DPT-BE

**14. RAC# 2061045: Comparison between two different laboratory test for the detection of Heparin Induced Thrombocytopenia**

**Investigators:** Dr. Randa Al Nounou

The objective of the study is to assess the performance of particle gel Immunoassay(PaGIA) and Enzyme-linked immuno-sorbent assay (ELISA) in the diagnosis of Heparin Induced Thrombocytopenia (HIT). The other objective is to evaluate the need to develop more rapid testing strategies with greater specificity for clinical HIT.

# **PEDIATRICS**



## The Department of

# PEDIATRICS

The value of clinical research is well understood where advance in medicine is based largely on basic and clinical research translated into practice. Clinical research is considered complementary to good clinical practice by stimulating creativity of researcher, sharpen their skills, and provide local experience. Conducting research in our community is a challenge due to lack of funding, appropriate supports, and lack of skills sometimes.

*Chairman*  
Saleh Al Mofada, MD

This report summarizes research activities at Department of Pediatrics. Despite the fact that majorities of these studies were retrospective, these represent genuine motivation of those physicians towards conducting clinical studies and bring about local experiences. Collaboration among physicians and scientists at Research Centre has brought up excellent project illustrated by some of research submitted. The Department of Pediatrics is motivating research activity through holding Pediatric Research activity and participation with combined MCO and Research Centre Research Day. We are working hard to build up research skills of the staff through educating and involving junior physicians in research projects. In addition, serious attempts are in place to open a new venue to fund and support new research ideas. We are sure that multifaceted efforts will bring about research mileage in which innovation idea easily survive.

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## RESEARCHACTIVITIES

### 1. Underlying Molecular Defects of Chronic Granulomatous Diseases (CGD) in a Cohort of Saudi Patients, RAC 2070017.

**Investigators:** Saleh Al-Muhsen, MD, Osama Alsmadi, PhD, Abdulaziz Al-Ghoniaum, MD, Hamoud Al-Mousa, Hasan Al-Dhekry, MD, Sulaiman Al-Gazlan, MD, Hasan Al-Rayes, MD, Rand Arnaout, MD, Anas Al Azami, MD

Chronic granulomatous disease (CGD) is a primary immunodeficiency caused by genetic defect in one of the components of NADPH oxidase of the phagocytic cells. This system is important in combating catalase producing organisms such as many bacteria and fungi. In addition to susceptibility to infections, CGD patients are prone to non-infectious complications, as lymphadenopathy, hepatosplenomegaly, eczema, glomerulonephritis, and granulomatous colitis. The diagnosis of CGD is based on a compatible clinical presentation and demonstration of a defective respiratory burst. Several methods detect the production of reactive oxidants such as nitroblue tetrazolium (NBT) and dihydrorhodamine 123 oxidative burst assay using flowcytometry (DHR). With limitation in these diagnostic methods, there is clear indication to confirm the diagnosis by molecular genetics through demonstration of specific genetic mutations in one of the structural components of NADPH oxidase which is routinely done world wide.

There are four genetic mutations involving the phagocytic oxidase system that has been identified to date. The most common is an XL-recessive defect in gp91phox. Three other forms caused by AR defect in the other components of the NADPH oxidase system, encoding P22phox, P47phox, and P67phox respectively. (5-10) Recent data from a large national US registry indicated the XL-recessive form tend to present earlier and follow more severe course.

As per previous RAC approved project, more than 40 patients are followed for chronic granulomatous disease in the immunology clinic at King Faisal Specialist Hospital & Research Centre. We aim from this study to look for the underlying molecular diagnoses for approximately 60 affected patients with CGD. We hope to discover new mutation or novel genes causing CGD phenotypes peculiar to our population. In addition we will examine the correlation between the genotype to different clinical

phenotypes in order to recognize those patients with severe disease who need to have stem cell transplantation performed at early stage of the disease to achieve better outcome. Finally proper genetic counseling and pre-implantation diagnosis and intervention for such lethal disease will never be achieved without identification of the genetic defect in a given family.

### 2. The Prevalence of Chorioretinal Lesions in Saudi Patients with Chronic Granulomatous Disease of Childhood (RAC 2041032).

**Investigators:** Saleh Al Muhsen, MD, Amal Al Hemidan, MD, Amer Al-Shehri, MD, Abdullah AL Herbi, MD, Abdulaziz Al-Ghoniaum, MD, Ibrahim Bin-Hussain, MD

Chronic granulomatous disease (CGD) is a primary immunodeficiency caused by genetic defect in one of the components of NADPH oxidase of the phagocytic cells. Recent report indicated that chorioretinal lesions are more common than previously appreciated. We described for the first time the prevalence of ocular manifestations in a cohort of Saudi patients diagnosed with CGD.

The medical records for all CGD patients attending the immunodeficiency clinic from Jan 2004 to Dec 2006 at KFSHRC, Riyadh, Saudi Arabia were reviewed. All alive and accessible patients underwent full detailed ophthalmic examination by a single investigator (A.H.). Patients with chorioretinal disease were investigated for other causes of chorioretinitis as CMV infection, sarcoidosis, tuberculosis, syphilis, and vasculitis. Negative results were necessary to qualify for the study.

Among 32 CGD patients, 14 had abnormal eye findings (44%). Nine patients had either anterior segment disease (15.6%) or seborrheic blephritis (12.5%) one patient had upper eyelid abscess. Chorioretinal lesions were found in 4 patients (12.5%). All patients affected with chorioretinal lesions were boys and 2 of them had other male siblings also affected with CGD which might indicate an X-linked pattern of inheritance. The chorioretinal lesions in all patients were uniformly similar and consisted of hypopigmented, atrophic "punched out" chorioretinal scars around the arcades and mid-equator and always sparing the macula which appeared healthy as well as the optic nerve head. Photographs were obtained and it will be shown. One patient had an exudative hemorrhagic total retinal detachment in the right eye and multiple discrete chorioretinal lesions

around the arcade, inactive in nature and sparing the macula in the left eye. Unfortunately, final visual outcome of this patient was No Light Perception (NLP) in the right eye and only Light Perception (LP) vision in the left eye.

Eye manifestations are commonly found in CGD patients. Chorioretinitis which could be serious enough to cause vision loss is not uncommon complication. Therefore CGD patients should be screened regularly for CGD chorioretinopathy. Long term follow-up studies are required to better understand the natural history of this complication and will allow for more established preventive and therapeutic interventions.

### **3. The Outcome Of Hemopoietic Stem Cell Transplantation In Severe Combined Immunodeficiency Diseases (SCID): KFSH&RC Experience Compared To International Data. RAC 205052.**

**Investigators:** Saleh Al Muhsen, MD, Mouhab Ayas, MD, Nouf Al Khamees, MD, Atef Al Booq, MD, Abdulaziz Al Ghoniaim, MD, Hassan Shaheen, MD, Hamoud Al Mousa, MD, Hassan Al Dhekri, MD, Rand Arnaout, MD, Abdullah Al Jefri, MD, Amal Al Seraihy, MD, Hersi A, MD, Hassan Al Rayes, MD Hassan El Solh, MD.

Transplantation of hematopoietic stem cells provide cure for severe combined immune deficiency patients. Data on long-term outcome of this treatment in our area is limited. Therefore, our objective was to determine the impact of stem cell transplantation on long-term outcome in patients with severe combined immune deficiency syndrome.

108 transplants in 100 SCID patients have been performed between Jan 1993 to Dec 2006. 54% were T-B- SCID, 13% were T-B+ SCID, 13% were ADA deficiency, 9% were Omenn syndrome, 6% were CD8 Lymphopenia, and 5% were unclassified with severe T cell dysfunction. The overall survival with sustained engraftment at the time of analysis was 83%. Patients with T-B+ (91% survival) had better prognosis than T-B- SCID (83% survival). Transplant from HLA- Genoidentical matched donor was associated with the best outcome (89% survival). On the other hand ADA deficiency had the worst outcome (71%). Patients received reduced intensity conditioning before stem cell transplantation had the most favorable outcome (95% survival), while non-conditioned patients had lower survival rate (83%). The worst prognosis as expected for patients received myelo-ablation (70% survival). However, among

those who survived; patients received myelo-ablative chemotherapy had more stable engraftment and better immune reconstitution. Immune reconstitution and chimeric studies will be shown.

Hematopoietic stem cell transplantation provides long-term cure and survival for SCID. Whenever available, genoidentical HLA matched donor is the best source for stem cells. Myelo-ablation is not indicated for matched related HSCT in SCID and can cause unnecessary morbidity and mortality. Reduced intensity conditioning might be an option especially if it correlated with stable engraftment and long-term immune reconstitution. Further prospective long-term studies are required.

### **4. Underlying Molecular Genetic Defects Of Severe Combined Immunodeficiencies (SCID) In Saudi Arabia, RAC 2060120.**

**Investigators:** Hamoud Al-Mousa, Osama Alsmadi, Abdulaziz Al-Ghoniaim, Hasan Al-Dhekri, Hassan Al-Rayes, Saleh Al-Muhsen, Rand Arnaout, Abdelghani Tbakhi, Dorota Monies, Salma Wakil

Severe combined immunodeficiencies (SCID) represent the most severe form of primary Immunodeficiencies. At least ten different forms of human SCID have now been recognized and can be grouped according to inheritance, phenotype, and for some of them, identification of the mutated genes. All SCID phenotypes are seen in the Kingdom, but up to date the underlying molecular genetic defects of those patients are not identified. The specific aim of this study is to identify the underlying molecular genetic defects of SCID in Saudi Arabia. All retrospective and prospective patients with the diagnosis of SCID under follow-up at KFSH&RC in primary immunodeficiency clinics or the post bone marrow transplantation clinic will be identified. Based on SCID phenotype, individuals will be screened for mutations in most likely genes that fit the clinical and laboratory presentation of SCID. Up to date, more than 40 families with SCID disease had been studied; mutations in RAG1, RAG2, Artemis, Jak3 and ADA genes have been identified; some were novel mutations. Families of patient's negative for mutations of the known SCID genes who demonstrate a strong family history will be utilized for subsequent linkage analysis depending upon statistical power of pedigrees and accessibility to family members that may identify novel genetic defects. It is expected that data resulting from this study will benefit future counseling and newborn screening programs.

### 5. Allogenic HLA-Identical Bone Marrow Transplantation In Major Histocompatibility Complex Class II Deficiency: A Single Center Study, RAC 2051049.

**Investigators:** Hamoud Al-Mousa, MD, Zamil Al-Shammari, MD, Samira Rifai, MD, Abdulaziz Al-Ghoniaum, MD, Hasan Al-Dhekri, MD, Hassan Al-Rayes, MD, Saleh Al-Muhsen, MD, Rand Arnaout, MD, Abdelghani Tbakhi, MD, Samer Markiz, MD, Ashraf Radwan, MD, Othman Mosleh, MD, Amal Al Seraihy, MD

Major Histocompatibility Complex Class II (MHC II) deficiency is a rare combined immunodeficiency disease characterized by profoundly deficient HLA class II expression, inconsistent and incomplete expression of HLA class I molecules, and lack of cellular and humoral immune responses to foreign antigens. Clinical manifestations include extreme susceptibility to viral, bacterial, fungal and protozoal infections, primarily of the respiratory and gastrointestinal tract. Severe malabsorption with failure to thrive ensues, often leading to death in early childhood.

MHC II deficiency has an autosomal recessive mode of inheritance. The majority of patients are of North African and Middle East origin although patients from other ethnic backgrounds had been reported. The diagnosis of MHC II deficiency in patients referred to immunodeficiency clinics at KFSH & RC with history of recurrent infections is not unusual. Disease has been noticed in certain tribes. The disease incidence at Saudia Arabia has not been studied yet.

The disease is due to defects in several distinct trans-acting regulatory factors required for expression of MHC II genes. Three of these genes, MHC2TA (OMIM number = 600005), RFX5 (OMIM number = 601863), and RFXAP (OMIM number = 601861), have been isolated and shown to be mutated in MHC II deficiency patients.

Allogeneic BMT is considered the only available curative treatment for MHC II deficiency. BMT can cure the disease, provided it is performed before complications leading to severe organ failure develop (Klein et al, 1995). The relatively low overall success rate of bone marrow transplantation when compared to some of the other forms of immunodeficiency (i.e., only a 54% survival rate following HLA-identical transplantation) possibly reflects the considerable heterogeneity in clinical presentation of these disorders and in the age at transplantation.

Two interesting observations have been made in long-term survivors of successful transplants (Klein et al, 1995): 1) persistence of a relative CD4 T cell lymphopenia – possibly due to a lack of HLA class II molecules on thymic epithelial cells – even though the donor derived CD4+ T cells are functional, and 2) defective expression of HLA class II molecules on non-hematopoietic cells appear to have no detrimental consequences.

### 6. Allogenic Bone Marrow Transplant In Leukocyte Adhesion Defect 1: A Single Center Study, RAC 2051053.

**Investigators:** Hassan Dhekri, MD, Abdulaziz Al-Ghoniaum, MD, Abdullah Al Jefri, MD, Hamoud Al Mousa, MD, Rand Arnaout, MD, Saleh Al Muhsen, MD, Abdelghani, Tbakhi, Mouhab Ayas, MD, Mohammed Mahr, MD, Lyla Osman, MD, Hasan Shahin, MD, Hassan Rayes, MD.

Leukocyte Adhesion Deficiency type 1 (LAD-1) is rare autosomal recessive immunodeficiency disorder characterized by delayed umbilical cord separation, omphalitis, impaired pus formation and wound healing, recurrent infections of the skin, upper and lower airways, bowel, and peri-rectal area, severe destructive gingivitis and periodontitis and persistent leukocytosis.

The severe phenotype is fatal unless bone marrow transplantation (BMT) is performed.

We present retrospective analysis of LAD-1 underwent bone marrow transplantation (BMT) over 20 years (1984-2004) in KFSH&RC.

Six patients with LAD-1 were transplanted, five were full match genodentical, one was haploidentical. Median age was 6.75 months at diagnosis, 10.1 months at BMT.

Conditioning regimen were cyclophosphamide and busulphan. Two patient received additional Campath and VP16+ATG respectively on the second BMT. Graft versus host disease (GVHD) prophylaxis were cyclosporine A (CSA) and methotrexate in 4/6, two received CSA only.

All genodentical patients engrafted, with mixed chimerism in 4/5 and full engraftment in one. CD18 expression as low as 15% is protective. One patient had acute grade 2 GVHD; none had chronic GVHD.

We concluded that full-match genodental BMT for LAD has an excellent outcome with a minimal GVHD complications.

### **7. The Outcome Of Hematopoietic Stem Cell Transplant For Wiskott-Aldrich Syndrome Patients: A Single Center Study, RAC 2051051.**

**Investigators:** Rand K. Arnaout, MD, Abdulaziz Al Ghonaium, MD, Hassan Al Rayes, MD, Saleh Al Muhsen, MD, Hasan Al Dhekri, MD, Hamoud Al Mousa, MD, Abdulghani Tbakhi, MD, Tareq Oweida, MD, Amal Al Seraihi, MD, Mohab Ayas, MD, Samira Al Rifai, MD, Hassan El Solh, MD

Wiskott-Aldrich Syndrome (WAS) is a rare mostly X-linked form of immunodeficiency characterized by thrombocytopenia, eczema, recurrent infections, autoimmunity, and an increased incidence of malignancy. Clinical severity is highly variable so is therapeutic modalities. Currently stem cell transplant with all its modalities is the only curative treatment. We retrospectively analyzed the results of our WAS patients at KFSH&RC from both Hematology/Oncology database and Immunology database between 1993-2006.

We had records of 22 Wiskott-Aldrich patients, 7 of which did not go for transplant for different reasons. 15 patients underwent stem cell transplant which is equivalent to 68%. Out of these 15 patients, only 1 patient had Marrow/Matched Unrelated Donor (MUD) transplant, 4 patients got Cord blood transplant, equivalent to (26.6%) with 50% survival and 10 patients got Allogenic BMT from related HLA-matched donor with 100% survival.

Our overall survival in our cohort of patients is 80%. All doing well. We have a 20% mortality rate most of the mortality is secondary to intracranial bleeding and or infection.

Our results are comparable to results from United States, Japan and Europe.

### **8. Short-Term Outcome Of Infants Less Than 1500 Grams: Local Experience, RAC 2071057.**

**Investigators:** Fahad Al Hazzani, Emad Khadawardi, Abdulhakiem Kattan, Saleh Al-Alaiyan

The outcome of very low birth weight infants (VLBW) is usually derived from publications mainly from North

America and Europe. In contrast, publications from Saudi Arabia in terms of the outcome of VLBW are scarce.

The aim of this study is to retrospectively collect data on the short term outcome of infants with birth weight <1500 grams managed at King Faisal Specialist Hospital and Research Centre. We want to compare our data to published international data.

Data of all live born infants with birth weight 400- 1500 grams who were admitted to the NICU at King Faisal Specialist Hospital and Research Centre were obtained from January 2006 to September 2007.

A total of 130 (117 inborn) preterm infants with birth weight < 1500 grams were recorded. Of these infants, 45% were males, 75 % of mothers received antenatal steroids, 80 % were delivered by CS. Mean GA was 28 weeks and mean BW was 1080. Major congenital anomalies were present in 10.8% of infants. The survival to discharge was counted to be 84.5 %. The complications of prematurity were as follows: RDS 74 %, PDA 33%, CLD 19.7%, NEC 10%, Sepsis 28.7 %, and IVH 11%; severe IVH 5 %, PVL 3%, and ROP 25.7% (Only one infant required ROP surgery).

The current data provide an idea about the short term outcome of VLBW infants at a local level. Our data were comparable to published international data.

### **9. Ethics Of Resuscitation At Different Ages Of Life, RAC 2071036.**

**Investigators:** Fahad Al Hazzani, MD, Saleh Al-Alaiyan, MD

Active resuscitation of a patient is often performed without consent because of an emergency context. At other times, informed consent may be obtained because there is sufficient time to have a discussion with the patient or his representatives. -Is it possible that clinicians will resuscitate patients at different frequency depending on the age of the patient and their personhood despite similar predicted outcome? Will extremely premature infants have a decreased frequency of resuscitation than children or adults with similar predicted outcomes?

An anonymous questionnaire will be distributed to individuals involved directly or indirectly with resuscitation decisions: residents, and physicians in pediatrics, obstetrics and adult medicine. This questionnaire has 8 different scenarios where patients with different

conditions have to be acutely resuscitated. Some of the patients have similar outcomes, but have different ages. One is asked if they would resuscitate the patient in the scenario, if they think it is in their best interest, and if they would do the same for them / their family.

#### **10. External Pressure Compression For Umbilical Hernia Management: Randomized Clinical Trial. RAC 2071 070.**

**Investigators:** Saud Al Sahanafey, MD, S. Qidawi, MD, Abdullah Al Dowaiish, MD, Fahad Al Hazzani, MD

Umbilical hernia is one of the most common abnormalities that affect infants. Although most physicians believe that umbilical hernias close spontaneously, few studies have documented the natural history of this condition. Few studies have attempted to test the utility of the external compression for the management of infantile umbilical hernia. We hypothesize that use of external compression promote early closure of the fascial defect in umbilical hernia patients. A randomized clinical trial design will be utilized. Infants younger than 6 months of age diagnosed with umbilical hernia will be randomized to either external pressure compression (group A) or expectant management (group B). Group A patients will have a compressive dressing applied over the umbilical hernia. The dressing will be changed every 48 hours. All patients will be followed up at 3 and 6 months after recruitment. Groups will be compared regarding the decrease of fascial defect, closure of fascial defect, and development of complications. Descriptive statistics will be generated for each group and compared. Means will be compared using student t-test, and proportions will be compared using Chi-square or Fisher's exact test where appropriate. Statistical analysis will be performed using SPSS statistical package, version 10.

#### **11. Intractable Diarrhea And Chronic Arthritis In 2 Saudi Families, RAC 2081006.**

**Investigators:** Nahla Alswaid, MD, Ali Almehaidib, MD, Suliman Al-Mayouf, MD

Chronic arthritis in children is a rare condition. Enteropathic arthritis is not commonly used; it is a descriptive term rather than a specific diagnosis. Most of the enteropathic arthritis is associated with evidence of systemic diseases. It can be either infectious or inflammatory conditions.

Rheumatic manifestations of diseases primarily of the gastrointestinal tract are frequent and variable. These manifestations include arthralgia, transient or destructive arthritis and osteoporosis.

The coexistence of intractable diarrhea and chronic arthritis starting in infancy is very rare and has limited possible underlying causes.

Inflammatory bowel disease (IBD) is a familial disease and can affect all age groups. However; it has not been well described in infants. IBD; ulcerative colitis, and Crohn's disease may present with chronic diarrhea and arthritis. This form of arthritis is classified as one of the group of seronegative spondyloarthropathies.

Celiac disease (CD) is a primary gastrointestinal disease with wide clinical spectrum. It may present with polyarthritis.

There are rare conditions characterized clinically by chronic diarrhea and non destructive arthritis. Biopsies from the colorectal mucosa showed a thickened subepithelial collagen layer consistent with collagenous colitis.

Infantile systemic hyalinosis (ISH) is a rare inherited disease of connective tissue characterized by widespread deposition of hyaline material in skin, musculoskeletal and deep organs including the gut in addition to nodules formation and joint contractures. Most of the patients failure to thrive with severe muscle wasting and intractable diarrhea.

Juvenile idiopathic arthritis (JIA) is the most frequent form of chronic arthritis in children. JIA rarely occurs as a familial disease, detailed family studies of patients and first-degree relatives have been published. Systemic onset subtype of JIA may associate with abdominal pain due to peritonitis but never associated with chronic diarrhea.

We followed 4 children with intractable diarrhea associated with chronic arthritis. The affected patients are siblings belonging to 2 different unrelated families.

The objective of this study is to report the clinical, biochemical and radiological features, and survival of 4 children with infantile intractable diarrhea and chronic arthritis.

**12. Familial Arthropathy In Saudi Arabian Children: Demographic, Clinical And Biochemical Features, RAC 2041080.**

**Investigators:** Suliman Al Mayouf, MD

Familial arthropathy is a descriptive term more than a specific diagnosis. It comprises different conditions. The frequency of these disorders worldwide is unknown, but it is considered not a rare condition. Familial arthropathy can be inflammatory or non-inflammatory conditions. Most of the familial arthropathies are not associated with evidence of systemic or localized inflammation. It is not unusual to label such conditions as having juvenile idiopathic arthritis, which is the most frequent inflammatory rheumatic disease in children. Although juvenile idiopathic arthritis rarely occurs as a familial disease, detailed family studies of patients and first-degree relatives have been published. The etiology and pathogenesis of juvenile idiopathic arthritis are not completely understood. Many studies point to a genetic component in the susceptibility for these diseases. We have followed a cohort of patients with different conditions of familial arthropathy. In this review, we focused on familial juvenile idiopathic arthritis and its comparison with sporadic type. We also studied the clinical and radiological features of two familial arthropathy syndromes presented with non-inflammatory joint manifestations. We did not include conditions traditionally considered to be familial rheumatic disease such as Spondyloarthropathies. We hope this review would alert the treating physicians to the clinical clues of the possibility of familial arthropathy and encourage searching for specific diagnosis.

**13. Cyclophosphamide (Cytozan) Use In Juvenile Systemic Lupus Erythematosus (JSLE), RAC 2041024.**

**Investigators:** Suliman Al Mayouf, MD and Abdullah Al Sonbul, MD

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease. It is characterized by the presence of autoantibodies and circulating immune complexes which give rise to tissue damage often resulting in end organ disease and even mortality <sup>1</sup>.

The incidence of SLE has nearly tripled in the period between 1950–1992 and there has been a statistically significant improvement in survival <sup>2</sup>. These are likely due to a combination of improved recognition of mild disease and better approaches to therapy.

Aggressive immunosuppressive therapy with cyclophosphamide has improved the outcome of major organ disease in lupus patients<sup>3</sup>. The two main indications for cyclophosphamide in lupus are active World Health Organization (WHO) class IV nephritis (diffuse proliferative glomerulonephritis) and neuropsychiatric lupus. However, it has been used to treat refractory disease irrespective of renal and central nervous system involvement.

The objective of this study is to report our experience with Cyclophosphamide treatment in children with systemic lupus erythematosus and to look at the safety and efficacy after the completion of the treatment course. The efficacy will be evaluated by the incidence of disease flare (i.e. symptoms recurrence and laboratory disease activity markers), incidence of renal impairment, renal failure and end stage renal disease during or after treatment completion as well as the improvement or deterioration of the concerned symptoms related to the affected organs.



# **PEDIATRIC HEMATOLOGY/ONCOLOGY**



The Department of

# PEDIATRIC HEMATOLOGY/ ONCOLOGY

*R*esearch activity in the Department has continued to grow. There has been the beginning of a move from retrospective review to development of prospective study of our patients and their outcomes. This has certainly been assisted by the establishment of the Central Data Unit, and by the desire of the staff for better quality research. We have continued to foster and expand our research collaboration with the Research Center and with other sister Departments in the Hospital. The fruits of this endeavor will clearly be visible in the forthcoming years.

Several ongoing translational research studies that are being conducted in collaboration with the Research Center are reaching maturity and are expected to furnish their results for publication within the coming year. As can be seen in the list below, several studies were presented at international conferences in abstract form. While these do not contribute to the list of publications, they do serve as an indicator for the ongoing research activity in the Department.

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*Director*  
Mohammed Al-Mahr, MD

## PUBLICATIONS

- Al-Aidarous A, Bin-Hussain I, El-Solh H, Kofide A, Thawadi S, Belgaumi A, Al-Ahmari A. Invasive *Chaetomium* infection in two immunocompromised patients. *Pediatr Inf Dis J*, May 2007; 25 (5):456-8.
- M. Ayas, A. Al Musa, A. Al Jefri, A. Al Seraihi, M. Al Mahr, S. Rifai, H. El Solh. Allogeneic stem cell transplantation in a patient with dyskeratosis congenital after conditioning with low-dose cyclophosphamide and anti-thymocyte globulin. *Pediatric Blood & Cancer*. July 2007; 49 (1): 10-104.
- A. Al Seraihi, M. Ayas. Hyperbaric oxygen should not be used in the management of hemorrhagic cystitis in patients with Fanconi anemia. *Pediatric Blood & Cancer*. November 2007; 49 (6): 854-856.
- Abubaker J, Bavi P, Al-Harbi S, Mourad W, Al-Dayel F, El-Solh H, Ezzat A, Uddin S, Al-Kuraya K. PIK3CA mutations are mutually exclusive with PTEN loss in diffuse large B cell lymphoma. *Leukemia*. 2007; 21:2368-70.
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- M. Ayas, A. Al-Ghoniaim. In patients with chediak-higashi undergoing allogeneic SCT, does adding etoposide to the conditioning regimen improve the outcome? Letter to the editor. *Bone Marrow Transplantation*, 2007, 40: 603.
- M. Ayas, A. Al-Jefri, A. Al-Seraihi, M. Al-Mahr, S. Rifai, A. Al-Ahmari, A. Khairy, I. El-Hassan, H. El-Solh. Allogeneic Stem Cell Transplantation in Fanconi Anemia Patients Presenting with Myelodysplasia and/or Clonal Abnormality: Update on the Saudi Experience. *Bone Marrow Transplantation*, 2007, Nov 5; [Epub ahead of print]
- H. Frangoul, E. Nemececi, D. Billheimer, M. Pulsipher, S. Khan, A. Woolfrey, B. Manes, C. Coles, M. Walters, M. Ayas, Y. Ravindranath, J. Levine, S. Grupp. A prospective study of G-CSF primed bone marrow as a stem cell source for allogeneic bone marrow transplant in children: a Pediatric Blood and Marrow Transplant Consortium (PBMTTC) study. *Blood*, 2007, 110: 4584-4587.

## ABSTRACT PRESENTATIONS

- A. Al-Jefri, M. Ayas, A. Al-Musa, M. Al-Mahr, M. Saleh, S. Rifai, R. Sabbah, A. Al-Seraihi, A. Al-Ahmari, A. Khairy, I. Al-Hassan, H. El-Solh King Faisal Specialist Hospital (Riyadh, SA). Allogeneic stem cell transplantation in patients with thalassaemia: the Saudi experience. Poster presentation No. 418 at the EBMT 2007 congress to be held in Lyon, France, March 25 - 28, 2007.
- S. Rifai, M. Ayas, I. Al-Fawaz, Z. Habib, S. Al-Sheneifi, A. Al-Seraihi, A. Al-Jefri, Y. Khafaga, A. Al-Ahmari, M. Al-Mahr, H. El-Solh King Faisal Specialist Hospital (Riyadh, SA). Megadose chemotherapy followed by autologous stem cell transplantation in patients with high-risk neuroblastoma, the experience of a specialist hospital, Saudi Arabia. Poster presentation No. 179 at the EBMT 2007 congress to be held in Lyon, France, March 25 - 28, 2007.
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## ACTIVE RESEARCH STUDIES

1. P. Glycoprotein in Childhood Leukemias in KSA. A Prospective Study of Expression and Correlation with Outcome. Al-Nasser A, et al. RAC# 2001004.
2. Flow Cytometric Analysis in Childhood Acute Lymphoblastic Lymphoblastic Leukemia (ALL) in KSA: A Prospective Study Of Expression And Correlation With Outcome (Min Res D). Al-Nasser A, et al. RAC# 2001007
3. The Expression of MMP-9, TIMP-1 and Correlation of TIMP-1 and IL-10 in Pre-B Pediatric Acute Lymphoblastic Leukemia. Al-Nasser A, et al. RAC# 2010029.
4. Translational Initiatives in Lymphoid Malignancies. Belgaumi A, et al. RAC # 2020015.
5. Pharmacokinetics of Methotrexate in Children with Acute Lymphoblastic Leukemia: Correlation

19. Prospective Evaluation of Risk-Adapted Therapy for Pediatric Patients with Non-Lymphoblastic Non-Hodgkins Lymphoma. Belgaumi A, et al. RAC # 2051018.
20. Allogeneic Stem Cell Transplantation In Patients With Fanconi Anemia - The King Faisal Specialist Hospital And RC Experience. Ayas M, et al. RAC # 2061037.
21. Chemo-reduction In Retinoblastoma. Al-Kofide A, et al. RAC # 2061040.
22. Where Do We Stand With Chronic Immune Thrombocytopenia In Children? A KFSHRC Riyadh Experience. Sathiapalan R, et al. RAC # 2071012.
23. Allogeneic Stem Cell Transplantation In Patients With Fanconi Anemia Using Further Reduced Doses Of Cyclophosphamide With Addition Of Fludarabine. Ayas M, et al. RAC # 2071037.
24. The Outcome of Children with Aml Post Post Allogeneic Sct - Comparison between Two Conditioning Regimens. Ayas M, et al. RAC # 2061076.
25. The Use of Reduced Intensity Regimen In The Conditioning Of Patients With Immune Deficiency Disorders Undergoing Allogeneic Stem Cell Transplantation (SCT). Ayas M, et al. RAC# 2061057.
26. Allogeneic Stem Cell Transplant for JMML: Single Institution Experience. Al-Ahmari, et al. RAC # 2071048.
27. The Outcome of Children with Constitutional Single Cytopenia Post Allogeneic STC from Matched Related Donor: Single Centre Experience. Al-Ahmari, et al. RAC # 2071049.

# **RENAL TRANSPLANT UNIT**



The

# RENAL TRANSPLANT UNIT

The Hospital has the largest Renal and Pancreas Transplant Program in the Kingdom and in the Region. On average, 140 kidney transplants are done annually. The scope of our services is quite diverse and includes: Transplanting highly sensitized patients with positive cross-match; low body weight pediatric patients; and kidneys with difficult vascular anastomosis (en-bloc kidneys, kidneys with multiple services, small sized kidneys). The above services can only be offered at KFSH&RC.

We have recently started solid organ pancreas transplantation simultaneously with or after kidney transplantation for patients with Type I diabetes mellitus. We are the only program in the Region that does such transplants. Seven transplants have so far been performed.

The Renal and Pancreas Transplant Program at KFSH&RC as such measures up to the top 10% of international renal transplant programs.

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**Director**  
**Khalid Al Meshari, MD, FACP**

### **Members**

- Khaled Hamawi, MD, Consultant
- Ammar Abdulbaki, MD, Consultant
- Hassan Al Eid, MD, Associate Consultant
- Hazem El Gamal, MD, Assistant Physician
- Ihab Mahmoud, MD, Assistant Physician
- Ashref Attia, MD, Assistant Physician

## RESEARCH PROJECTS

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### 1. Islet Cells Transplantation: Collaboration Between Geneva University Hospital And King Faisal Specialist Hospital And Research Centre (Following Edmonton Protocol).

**Investigators:** Abdulrahman Al Nuaim, MD, Khalid Al Meshari, MD, Hussein Raef, MD, Ahmed Chaballout, MD, Hamad Al Suhaibani, MD, Abdelghani Tbakhi, MD, Aman Al Fadhli, MD, Khaled Hamawi, MD

#### Project description

Performing islet cells transplantation in selected subgroup of type I diabetic subject following Edmonton immunosuppressive protocol. Isolation of islets is done in collaboration with university of Geneva.

#### Progress

To date, two patients have been selected. Arrangements with Saudi Center for Organ Transplantation (SCOT) and University of Geneva has been finalized. A new islet cell isolation lab at KFSH&RC was established.

### 2. Proposal # 2041 081 - Determination of polymorphism (S) in genes controlling the immune responses in Saudi renal transplant patients

**Investigators:** Khalid Al Meshari, MD, Abdelghani Tbakhi, MD, Khalid Al Hussein, MD

#### Project description

Examining the features and polymorphism of some of the immune genes such as MHC, cytokines and KIR genes

in relation to renal transplant outcome.

#### Progress

Patient sera were collected. Standardization of laboratory methodology in Research Center has been documented.

### 3. Proposal # 2071 013 - A Study Of The Pathogenic Role's Of Hepatitis C Virus (HCV) Infection In The Development Of Post-Renal Transplant Diabetes Mellitus

**Investigators:** Khalid Al Meshari, MD, Ismail Ibrahim, MD

#### Project description

Studying the risk factors of post-renal transplant diabetes mellitus (PTDM). Amongst these risk factors is HCV infection. Digging deeper for the HLA typing in the hepatitis C virus patients who are going to be prone and susceptible to develop PTDM.

#### Progress

Proposal recently been approved by the Clinical Research Committee (CRC).

#### Future Research Direction

We are in the process of implementing a new database system for renal transplant recipients. This will allow us to conduct a number of studies to evaluate our current medical practice and to direct future improvements.

Future studies will focus on survival data and innovative immunosuppressive protocols.

# UROLOGY



The Department of

# UROLOGY

The Department of urology aims to create a research community for major urologic diseases and syndromes within the KFSH&RC mission interests. It's broad objectives are to: 1) provide an interdisciplinary and multidisciplinary foundation and resource for collaboration among basic, translational, and clinical researchers in the field of urologic disease; and 2) attract investigators with unique scientific expertise and new investigators to study urological diseases and disorders

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*Chairman*  
**Kamal A. Hanash, MD, MS (Urology), FACS**

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## RAC-APPROVED RESEARCH ACTIVITIES

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**Project title: Optimization of *Tunica Albuginea* Free Graft for Corporoplasty: An Experimental Animal Study. RAC Approved # 2031 086**

**Investigators:** Dr. Raouf Seyam, Dr. Alaa Mokhtar, Dr. Kamal Hanash, Dr. Walid Mourad, Dr. E. Chisti, Dr. F. Al Mohanna, Dr. R. El Sayed

Identification of the qualities of free *tunica albuginea* graft for the correction penile curvature and shortening that is associated with Peyronie's disease. This entails evaluation of the effect of the graft on the hemodynamics of erection, development of erectile dysfunction and the risk of fibrosis affecting the graft and underlying cavernous tissue.

We have performed 10 surgeries of free graft implantation of the size 1x3.5 cm. Six-month follow-up was reported in our abstract presented to the American urological association (AUA). One year results were published in the *Journal of Sexual Medicine*. Two more animals were subjected to fibrin glue injection for developing Peyronie's disease model. Both animals developed curvature of the penis up to 45% at 3 months, which is consistent with our proposal. More animals will be used to study different sizes of free graft in healthy and Peyronie's disease animal model.

**Project title: UroLume Urethral Stent for the Treatment of Bladder Outflow Obstruction: A Long Term Retrospective Review. RAC Approved # 2041 072**

**Investigators:** Dr. Muhammad Aslam, Dr. Kamal A. Hanash, and Dr. Irfan Ahmed

The UroLume was first used to treat urethral strictures in 1987, soon thereafter the indications expanded to include the treatment of benign prostatic hyperplasia (BPH), detrusor sphincter dyssnergia (DSD) in spinal cord injured patients, vesicourethral anastomotic strictures (bladder neck contracture) following radical retropubic prostatectomy and to treat bladder outflow obstruction after transperineal brachytherapy for carcinoma of the prostate.

The rationale behind the study is to retrospectively review the charts of all patients who underwent UroLume endoprosthesis insertion between 1975-2004 and to evaluate the parameters like patient selection criteria,

indications, complications, patient satisfaction and long term efficacy of UroLume endourethral stent in bladder outflow obstruction.

**Project title: Artificial Urinary Sphincter Implantation for Urinary Incontinence: A Retrospective Long-Term Review. RAC Approved # 2041 083**

**Investigators:** Dr. Muhammad Aslam, Dr. Kamal A. Hanash, and Dr. Irfan Ahmed

Artificial urinary sphincter (AUS) implantation is an effective treatment for intrinsic sphincter deficiency resulting from radical prostatectomy, transurethral resection of prostate (TURP), severe female stress incontinence, neurogenic conditions, trauma and radiation to pelvis and spinal cord leading to sphincter deficiency and congenital abnormalities like myelomeningocele. Currently, majority of these devices are implanted in the patients who are incontinent after radical prostatectomy. Although a proportion of patients rarely require surgical revision to maintain continence, little actuarial data have been published to indicate the likelihood of the revision at specific intervals.

The aim of the study is a retrospective review to evaluate patient selection criteria, indications, surgical technique (cuff around bulbous urethra or bladder neck), complications, and to evaluate actuarial revision rate after TURP and radical prostatectomy, AUS safety, and reliability.

**Project title: The Effect of Alpha Adrenergic Blockers on the Ureter: An *In Vivo* Study in the Dog. RAC Approved # 2050 032**

**Investigators:** Waleed Al Taweel, MD, Kamal A. Hanash, MD, Rayouf Seyam, MD, Alaa Mokhtar, MD, Raafat El Sayed, MD, Falah Al Mohanna, MD, and Naser Elkum, MD

Alpha 1 – adrenergic blockers have been used clinically with variable degrees of success to ease the spontaneous passage of ureteral stones. The mechanism by which these medications affect the ureter and how they differ in efficacy is not known. We intend to study the effect of alpha-blockers on ureteral function in partial and complete obstruction in the anesthetized dog.

Male mongrel dogs weighing 8 to 12 kg under general anesthesia are used. The ureters are exposed and complete and partial ureteric obstruction is created

around cannulas connected to pressure transducers. The ureteric pressure, peristaltic waves, vesical pressure, blood pressure and heart rate are recorded simultaneously. Increasing concentrations of tamsulosin, terazocin, doxazosin and alfuzosin are administered intraduodenally. Each animal will be used for one drug and one dose and observed for 240 minutes after the first drug administration. The dosage are selected based on experiments on the effect of alpha blockers on urethral pressure. Intraduodenal administration produces peak plasma concentration within 30 minutes which correlates with maximal inhibition of intraurethral pressure. We anticipate that in this setting, we will be able to study the effect of these drugs on the ureter. Alpha-blocker adjuvant treatment to ureteric stones is worthwhile because it facilitates their spontaneous passage leading to decreasing complications, less intervention and less analgesic use. In this study, we compare the efficacy of these drugs and how they affect the ureter.

More animals will be tested and determination of the blood level of tamsulosin will be documented to establish that our results are due to absence of drug effect and not failure of absorption from the duodenum. We will need 12 more animals, 6 for saline control and 6 for tamsulosin.

**Project title: Incidence of Urinary Incontinence in Saudi Women. RAC Approved # 2051 071**

**Investigators:** Waleed Al Taweel, MD, Alaa Mokhtar, MD, and Raouf Seyam, MD

Urinary incontinence (UI) is a relatively common condition in middle-aged and older women. Traditional measures of symptoms do not adequately capture the impact that UI has on individuals' lives. Further, severe morbidity and mortality are not associated with this condition. Rather, UI's impact is primarily on the health status and health-related quality of life (HRQOL) of women. The objective of this study is to investigate the incidence of urinary incontinence (UI) symptoms in Saudi women presented to the outpatient polyclinic of King Faisal Specialist Hospital and Research Centre. Two validated questionnaires will be utilized.

Summary of the results of prevalence of urinary continence:

- 2182 completed the questionnaires
- The mean age 30±10 years

- 63% optimal weight and 33% over weight or obese
- 52% married and 48% single
- The prevalence of urinary incontinence was 29%
- 28% urge incontinence, 22% mixed, 50% stress incontinence
- Age, vaginal delivery, DM, large baby birth weight, higher BMI are potential risk factors for urinary incontinence. However, only 9% of incontinent women visited the doctor and the impact of incontinence on quality of life was not very high on Saudi women.

**Project title: Outcome of Proximal Hypospadias Repair. RAC Approved # 2061 005**

**Investigators:** Ahmed Al Mathami, MD, Kamal A. Hanash, MD, Mohammed Alabdulaaly, MD, Riad Farhoud, MD, and Raouf Seyam, MD

Hypospadias is one of the most common congenital anomalies that seen in pediatric urology with estimated prevalence of 3 to 8 cases per 1000 male birth. The malformation is the result of incomplete fusion of the urethral folds, which usually occurs between 9 to 12 weeks of gestation, although the success rate for hypospadias repair is high, the high prevalence translates into a significant financial burden and the health care system, when complications do occur, the resultant morbidity of corrective procedure, psychologic stress can be devastating to the patient and family.

Great advances have been made in surgery for the correction of hypospadias remains the greatest challenge, but despite many innovations and much progress surgery can fail, many authorities have introduced different type of repair to improve the result.

On this study, we review the outcome of proximal hypospadias repair (initial diagnosis, age at repair, pre-op evaluation, type of repair, post-op complications follow up, look to the result and the best to improve the outcome.

**Project title: Predictors of Viable Germ Cell Tumor in post Chemotherapy Mass for Metastatic Testicular Cancer. RAC Approved # 2061 021**

**Investigators:** Dr. Khalid Al Othman and Dr. Mohammed Al Mosa

Patients with metastatic germ cell testicular cancer may be cured by cisplatin-based chemotherapy. The residual retroperitoneal mass after chemotherapy

can be necrosis, mature teratoma or viable cancer cells. Surgical resection is a generally accepted treatment to remove residual tumor (mature teratoma or viable cancer cell) but resection of necrosis is not beneficial. In view of the well described complications of retroperitoneal lymph node dissection (RPLND) in patients with residual disease, patient selection plays an important role in excluding those who are unlikely to have viable disease.

We propose to undertake a study to identify reliable predictors for residual disease in patients with germ cell tumor who have residual retroperitoneal mass after chemotherapy treatment. It would avoid unnecessary RPLND with its significant surgical morbidity.

**Project title: Quality of Life Among Saudi Prostate Cancer One Year or More After Treatment. RAC Approved # 2071 043**

**Investigators:** Dr. Ali Bin Mahfooz, Dr. Hamad Al Helo, and Dr. Abdulaziz Al Mannaa

Quality of life (QOL) has been recognized as an important outcome of medical treatment and has become a core issue in health care systems. QOL is a concept encompassing a broad range of physical and psychological characteristics, which describe an individual's ability to function and to derive satisfaction from doing so. The increasingly strong interest in evaluating QOL outcomes in clinical research is imperative. To a large degree, this interest reflects the growing recognition that QOL is, in the vast majority of cases, the single most important clinical and research outcome. The true impact of a successful medical intervention can be understood to largely reflect the degree to which said treatment has a positive influence on patient's immediate and/or future well-being. By emphasizing the assessment of QOL in medical research, health care providers are being subtly encouraged to give proper focus to patient's welfare. Consequently, medical research and care is slowly becoming more patient-focused, and there is a growing appreciation of the patients' perspective on health, disease, and medical treatments. In Saudi Arabia, there were 156 newly diagnosed prostate cancer in 2001. The purpose of this study is to describe quality of life among Saudi prostate cancer patients one year or more after treatment.

Specifically, this study will answer the following questions:

1. What is the level of quality of life among Saudi prostate cancer patients as measured by Ferrans and power Quality of Life index-Cancer III version?
2. What demographic and disease related variables correlate significantly with quality of life?

**Project title: Arabic Validation of the Short Form of Urogenital Distress Inventory (UDI-6) Questionnaire. RAC Approved # 2071 050**

**Investigators:** Dr. Waleed Al Taweel, Dr. Alaa Mokhtar, and Dr. Raouf Seyam

The aim of the study is to translate and validate the Arabic version of the short form of Urogenital Distress Inventory (UDI-6) questionnaire in a sample of women with lower urinary tract symptoms (LUTS).

Two native Saudis will independently translate the original Urogenital Distress Inventory questionnaire (UDI-6) into Arabic. These two translations will be harmonized, and then checked by (independent-back) translation by two English teachers. They will collaborate with the clinical investigators to reach a consensus version of the questionnaire. The harmonized version will be pre-tested in a pilot study on 20 patients. Then the final version of the UDI-6 will be applied to another group of patients aged 22 years or over complaining of lower urinary tract symptoms (LUTS) for at least 3 months at King Faisal Specialist Hospital and Research Centre (KFSH&RC). The patients will be re-rated after 1 week to assess test-retest reliability. To assess the capacity of the questionnaire to discriminate between women with and without LUTS, cases and controls of healthy women sample will be involved and assessed. The psychometric properties of the questionnaire, such as reliability and validity will be assessed. The aim of this study is to validate the UDI-6 in the Arabic language by evaluating convergent and discriminate validity, test-retest reliability and internal consistency, in a specific group of female patients with lower urinary tract symptoms (LUTS) referred to King Faisal Specialist Hospital & Research Centre.

This Annual Research Report has been compiled and edited by the

**OFFICE OF RESEARCH AFFAIRS**

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