

annualresearchreport



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

This page was left intentionally blank.

THE KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE

ANNUAL RESEARCH
REPORT 2008

This page was left intentionally blank.

ACKNOWLEDGEMENTS

THIS BOOK HAS BEEN MADE POSSIBLE THROUGH THE HARD WORK AND
CONCERTED EFFORTS OF THE FOLLOWING STAFF OF THE OFFICE OF RESEARCH
AFFAIRS AND RESEARCH CENTRE:

MOHAMED M. AL TURKI, CCRP
ABEER HASSAN AL SAYED, MD
GHADA AL HAWSAWI, HRA
DERRICK G. MENDOZA, MD
CHIE MIRANDA
GRACE DELA TORRE
HAKEM AL-ENAZI
TALAL AKIF
IBRAHIM ALI MOHAMAD
MELVIN VELASCO

This page was left intentionally blank.

OUR MISSION

IS TO BE A CENTRE OF EXCELLENCE IN BIOMEDICAL RESEARCH.

WE ARE DEDICATED TO THE ADVANCEMENT OF SCIENCE AND THE TRANSLATION
OF RESEARCH FINDINGS INTO BETTER HEALTHCARE.

WE STRIVE TO PROVIDE AN ENVIRONMENT THAT ENHANCES INDIVIDUAL GROWTH,
COLLABORATION, ACHIEVEMENT AND RECOGNITION.

OPENING REMARKS FROM HIS EXCELLENCY

QASIM AL QASABI, MD, FRCSI, FACS

Chief Executive Director

King Faisal Specialist Hospital and Research Centre



The devotion and commitment of our investigators to the advancement of biomedical science is evident from their involvement in the cutting edge research programs and resulting scientific publications at reputable high impact journals. The quality of research conducted in our prestigious institution has significantly improved over the past few years.

One of the most noticeable achievements of our investigators is to establish collaborative links with renowned institutions around the globe. Likewise, many of our clinical investigators are now participating in several multi-centre randomized clinical trials. Our collaborative links and our involvement in international multi-centre clinical studies give a distinctive position for KFSH&RC in both local and international standards.

This Annual Report Book reflects our unwavering commitment to reach a higher level of success in all areas of research. I applaud the hard work and dedication of each and everyone in our mission to provide high quality healthcare in the Kingdom.

OPENING REMARKS FROM THE EXECUTIVE DIRECTOR OF THE
RESEARCH CENTRE

SULTAN AL-SEDAIRY, PhD

Executive Director
Research Centre

This Annual Report Book is a fitting accolade to the Institution's research achievements for the last twelve months. It highlights our zeal to achieve a higher level of success through non-stop research discoveries and innovation. Our activities are systematically and intricately designed to address the growing challenges in the advancement of science and technology. The publications released in several prestigious journals speak highly about our quest for quality healthcare. I salute our investigators and the many collaborators for their incessant support in our commitment to provide excellent output in all areas of research.



There is much work that awaits us! This report is just a tinge of what greater cooperation and collaboration can bring to the benefit of our patients and growing citizens in Saudi Arabia and people of the world at large. Let us continue to inspire one another for further continuity of our research programmes in a wider, comprehensive scope.

TABLE OF CONTENTS

THE RESEARCH CENTRE REPORT	1
The Office of Research Affairs / The Research Advisory Council	5
The Department of Biological and Medical Research	7
Allergy and Aerobiology	11
Breast Cancer	17
Carcinogenesis	21
Cell Biology and Confocal Microscopy	23
DNA Repair and Apoptosis	27
Environmental Health	31
Laser Medicine	35
Molecular Virology and Infectious Diseases	41
The Department of Biomedical Physics	47
Biomedical Physics Research	51
Clinical Dosimetry and Treatment Planning Unit	55
Gamma Irradiation Facility	57
Health Physics	59
Imaging Physics	61
Radiation Physics	63
Radiation Safety Office	67

Secondary Standard Dosimetry Laboratory	69
The Department of Biostatistics, Epidemiology, and Scientific Computing	71
Biostatistics Research Unit	75
Epidemiology Research Unit	95
Computing Services Core Facility	101
Registries Core Facility	105
Technical Databases Core Facility	113
The BioMolecular Research Program	119
The Centre for Clinical Studies and Empirical Ethics	125
The Department of Comparative Medicine	135
Experimental Surgery, Animal Facility Research Unit	141
Heatstroke & Cell Injury & Inflammation Research Unit	147
Laboratory Animal Facility	151
Microbial Immunology	157
Tuberculosis Research Unit	161
The Department of Cyclotron and Radiopharmaceuticals	165
The Department of Genetics	171
Cognitive Genetics (NeuroGenetics)	175
National Laboratory for Newborn Screening	181
The First Arabian Hereditary Deafness (FAHD)	185
Computational Genetics	187

Developmental Genetics	191
Saudi Diagnostic Laboratory	195
Genotyping Core Facility	197
Gene Therapy	199
Transcriptional Genetics	203
Cardiovascular and Pharmacogenomics Research Unit	207
Hereditary Immunology Unit	209
Behavioral Genetics	213
Sequencing Core Facility	217
The Department of Human Cancer Genomic Research	219
The Stem Cell Therapy Program	235
The Research Centre Training and Education Office	255
THE MEDICAL AND CLINICAL OPERATIONS REPORT	261
The Department of Dentistry	263
The Oncology Centre	269
The King Faisal Heart Institute	287
The Liver Transplant and Hepatobiliary and Pancreatic Surgery	303
The Department of Physical Therapy	307
The Department of Surgery	311

THE RESEARCH CENTRE
REPORT

This page was left intentionally blank.

THE
OFFICE OF RESEARCH AFFAIRS
AND THE
RESEARCH ADVISORY COUNCIL

The Office of Research Affairs / The Research Advisory Council

The Office of Research Affairs

The Office of Research Affairs (ORA) provides administrative support to the Research Advisory Council (RAC) and to KFSH&RC investigators conducting clinical or basic research.

THE GOALS OF THE ORA ARE TO:

- coordinate the activities of, and provide support to the Research Advisory Council;
- ensure compliance of research activities at KFSH&RC with applicable policies and to provide assurance of KFSH&RC compliance to regulatory bodies;
- obtain and administer external research funds for KFSH&RC investigators and to protect the interest of KFSH&RC and its investigators;
- protect inventions made at KFSH&RC and to help commercialize research results; and
- provide information to the public on research activities at KFSH&RC and on global scientific discoveries.

The Research Advisory Council

MISSION

The mission of the Research Advisory Council (RAC) is to promote, regulate, and monitor all aspects of research undertaken by members of, or within, the KFSH&RC.

CURRENT RAC MEMBERSHIP

Sultan T. Al Sedairy, PhD - Chairman
 Futwan A. Al Mohanna, PhD - Member and Coordinator
 Mohamed Al Turki, CCRP - Member
 Adnan Ezzat, MD - Member
 Muhammad M. Hammami, MD, PhD - Member
 Asim Belgaumi, MD - Member
 Abdelillah Aboussekhra, PhD - Member
 Ghazi Alsbeih, MD, PhD - Member
 Yufei Shi, MD - Member

SUPPORTING COMMITTEES

The Research Advisory Council is supported by five standing committees:

RESEARCH ETHICS COMMITTEE [REC]

Muhammad Hammami, MD, PhD - Chairman
 Zuhair Hassan, MD - Member
 Serdar Coskun, DVM, PhD, HCLD - Member
 Lamia Nounou - Member
 Walid Al Sous - Member
 Mohammed Al Sunaid, MD - Member
 Abdul Hamid El Bushra - Member
 Ayodele Abulkareem Alaiya, MD, PhD - Member
 Rana Al Moslimany, Bsc Pharm - Member

CLINICAL RESEARCH COMMITTEE [CRC]

Asim Belgaumi, MD - Chairman
 Michael Nester, PhD - Member
 Tarek Owaidah, MD - Member
 Nathem Akhras, PharmD - Member
 Habib Basil, MD - Member
 Walid Hassan, MD - Member
 Ahmed Helmy, MD - Member
 Ali Al Jubran, MD - Member
 Abdullah Al Dowaiish, MD - Member
 Rosemarie O'Neill Paradis, RN, MSNEA FACHE
 - Member

ANIMAL CARE AND USE COMMITTEE [ACUC]

Ghazi Alsbeih, MD, PhD - Chairman
 Subhani Okarvi, PhD - Member
 Raouf Seyam, MD - Member
 Salma Wakil Majid, PhD - Member
 Monther Al Alwan, PhD - Member
 Ranjit Parhar, PhD - Member
 Azhar Hussain, MBBS - Member
 Steve Bobis, DVM - Member
 Nahar Alanezi, MD - Member

BASIC RESEARCH COMMITTEE [BRC]

Abdelillah Aboussekhra, PhD - Chairman
 Nduna Dzimiri, PhD - Member
 Fowzan Al Kuraya, MD, PhD - Member
 Abdul Khalid Siraj, PhD - Member
 Mohamed Al Owain, MD - Member
 John Kotey Amartey, PhD - Member
 Claudia Walter, PhD - Member
 Hazem Ghebeh, PhD - Member
 Mohammad Qutub, MD - Member
 Mohamed Al Dosari, MD - Member
 Fahad Al Sharif, MD - Member

RECOMBINANT DNA COMMITTEE [RDC]

Yufei Shi, MD - Chairman
 Namik Kaya, PhD - Member
 Abdalla Al Haj, PhD - Member
 Mohammed Aldahmesh, PhD - Member
 Nisreen Al Moghrabi, PhD - Member
 Ra'afat El Sayed, DVM - Member

THE DEPARTMENT OF
BIOLOGICAL AND MEDICAL
RESEARCH

The Department of Biological and Medical Research

The discovery of knowledge through programs of basic and clinical research is continuously the high priority for the Department of Biological and Medical Research. With the branching out of the Stem Cell Therapy Program wherein four (4) sections in the BMR Department have been integrated into, the Department is now comprised of the following sections: Allergy and Aerobiology, Cell Biology and Confocal Imaging, Carcinogenesis, DNA Repair and Apoptosis, Environmental Health, Laser Medicine, Molecular Virology and Infectious Diseases. These sections are continuously working together in coordinated efforts leading to productive endeavours. Among our particularly strong disease-related research activities are those involved in the development of cancer and cardiovascular diseases. Our scientists will elaborate on their research activities and findings in the subsequent sections that follow.

During the year 2008, members of the Department have participated in giving an ongoing series of in-house lectures organized by the Research Centre Training and Education Office (RCTEC). The Department has also organized courses in coordination with RCTEC which were well attended. It continues to provide in-house and post-graduate training to interested students and graduates in collaboration with local academic institutions. Our scientific staff continues to contribute to the organization of national and international scientific conferences and workshops.

Acting Chairman:

Futwan Al-Mohanna, PhD, FIBiol, FRSC

Administrative Support Staff:

Jorge Bautista

Rita Sison

Robyn Seamer

Saif Zyada

Moneth Eborá

Cheryl Mijares

Ma. Cecilla Perez

Gina Gonzales

Hanan Shaarawi

MAJOR ACHIEVEMENTS FOR THE YEAR INCLUDE

- Discovered that curcumin is an enhancer of the killing effect of the anti-medulloblastoma agent cyclopamine.
- Demonstrated that the Atr protein kinase is a major regulator of the cellular response to UV damage and protects cells from UV-induced apoptosis.
- The majority of breast cancer stromal fibroblasts express low levels of the tumor suppressor Atr protein.
- Laser Therapy converts diabetic wound and burn healing to normal healing.
- Continuation of production of allergy diagnostic kits for the Middle East Region.
- Development of a community oriented services program for the people of Saudi Arabia
- Found the effect of dietary monosodium glutamate on trans fat-induced nonalcoholic fatty liver disease.
- Diabetes of the Liver: The Link Between Nonalcoholic Fatty Liver Disease and HFCS-55.
- Molecular typing of highly pathogenic avian influenza virus (H5N1).
- Studied the role of genetic polymorphisms in Toll like receptors in relation to HBV and HCV infection.
- Standardization of molecular diagnostic methods for detection of pathogens in various clinical samples.

SERVICE FOR FEE ACTIVITIES

1. Analysis of lead, cadmium, mercury, arsenic, antimony, nickel and chromium in cosmetics samples for the Saudi Food & Drug Authorities.
2. Analysis of mercury and hydroquinone in skin-lightening creams for the Saudi Food & Drug Authorities.

More information concerning each Section of the Department follows.

Allergy and Aerobiology

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

During the year 2008, our scientific activities remained focused on the following areas in research and development:

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

Head of Unit:

Syed M. Hasnain, PhD, FACAAl, FAAAAI

Members:

Halima Al-Sini, MSc

Abdulrahman Al-Sobhi

Mubarak Al-Enizi

Alanoud Al-Qassim

Assel Al-Otieschan

Samia Khan

RESEARCH PROJECTS/ACTIVITIES

Project Title: Isolation, Purification and Immunochemical characterization of allergenic proteins from *Amaranthus viridis* pollen grains, RAC #2050 029 approved by KACST for financial support under grant ARP 27-11.

Investigators: Syed M. Hasnain, PhD, FACAAl, FAAAAI, Abdulkareem Ayodele Alaiya, MB.BS, MPH, PhD, Mohammad Osman Gad-el-Rab, MD, and Mai Abdullah Al-Mohanna, PhD

The importance of the family *Amaranthaceae* pollen grain in triggering respiratory allergy is well known and documented. However, out of several species of *Amaranthus*, *A. viridis* is the most common in Saudi Arabia. A detailed study on *Amaranthus* Aerobiology in Saudi Arabia is already submitted for publication. The other *Amaranthus* species are either less prevalent or non-existent. Despite of their importance as a causative agent for different types of allergy, no thorough biochemical data are available on their allergenic proteins characterization. The information on the antigenic and allergenic components will be useful in the production of safe, effective and standardized diagnostics and therapeutic allergen extracts in the country. Biochemical and immunological characterization of allergen(s) proteins of *A. viridis*, the most prevalent weed in Saudi Arabia is currently underway.

In order to compare *in vivo* and *in vitro* allergenicity of *Amaranthus* species and cross-reactivities within the various species of amaranths, found in Saudi Arabia and in different parts of the world, commercial pollen grains of different species were purchased from various commercial suppliers in Europe and USA (Greer) (Allergon). In addition, Skin Prick Test (SPT) aqueous solutions were also purchased. These included:

- *Amaranthus palmeri*
- *Amaranthus retroflexus*
- *Amaranthus hybridus*
- *Amaranthus tuberculatus*

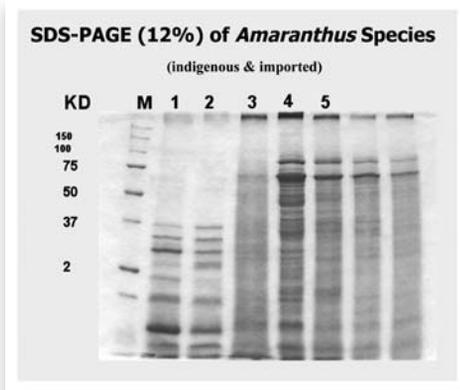
Indigenous *Amaranthus viridis* and other *Amaranthus* species were collected from different regions of Kingdom of Saudi Arabia these included: Riyadh, Jeddah, Taif, Makkah, Dammam, Dhahran, Hofuf, Abha, Najran, and Tabuk.

For skin prick test (SPT), extracts were prepared from pollen grains of these species (Indigenous and commercial). All species were defatted and extracted in buffered saline PH 8.1. proteins were estimated using GeneQuant1300, separation of protein was conducted by SDS- PAGE and 2D SDS-PAGE. The clinical studies will start this coming year as scheduled in the project.

Protein patterns of different types of *Amaranthus* samples were analyzed using two-dimensional polyacrylamide gel electrophoresis (2-DE). Global protein expression profile was evaluated by computer-assisted image analysis (PDQUEST) and potential proteins spots will be subsequently identified using MALDI-TOF-MS. The aim is to identify significantly differentially expressed protein and to further analyze the protein expression profiles by hierarchical clustering method among the different sub types of *Amaranthus*. The ultimate goal is to identify sets of proteins that are unique to each type of *Amaranthus* and their potential usefulness with be further evaluated for clinical use in development of vaccines.

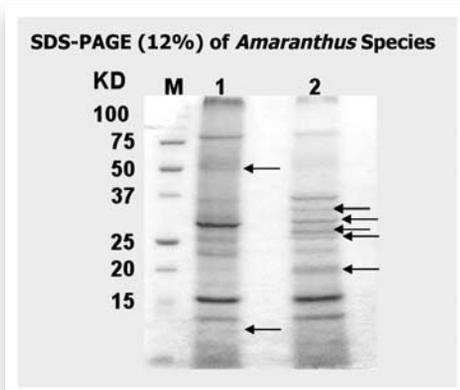
The initial studies indicate that the species of *Amaranthus* vary in their protein profile.

In the 2D gel images, an average of 447 protein spots was resolved among all different samples analyzed. Obvious qualitative similarities and differences were seen, however at least duplicate or triplicate gels will have to be run before marked quantitative differences can be determined to allow for significant statistical analysis, more biochemical studies are under investigation.



L1: *A. viridis* (20 µg), L2: *A. lividus* (18 µg), L3: *A. retroflexus* (Allergon) (30 µg), L4: *A. retroflexus* (Green) (40 µg), L5: *A. tuberculatus* (21 µg), L6: *A. hybridus* (20 µg), L7: *A. palmeri* (26 µg)

Figure 1: Remarkable differences between the protein profiles of the indigenous species (L₁, L₂) and the commercial species (L₃-L₇) are shown in the gel. The indigenous samples showed bands at lower molecular weight ranging between 36 KD & 14 KD, while the commercial species showed proteins at higher molecular weights.



M: Marker, L1: *A. viridis* (30 µg), L2: *A. lividus* (30 µg)

Figure 2: The difference between the two indigenous species is shown in this 12% SDS-PAGE Gel. Five bands were seen in the lane containing *Amaranthus lividus* at 34, 31, 28, 26 & 20 KD which did not appear in the lane containing *Amaranthus viridis*, indicating there is a variation in protein profiles within the indigenous species also.

REPRESENTATIVE 2-D GEL IMAGES FROM DIFFERENT AMARANTHUS SAMPLES

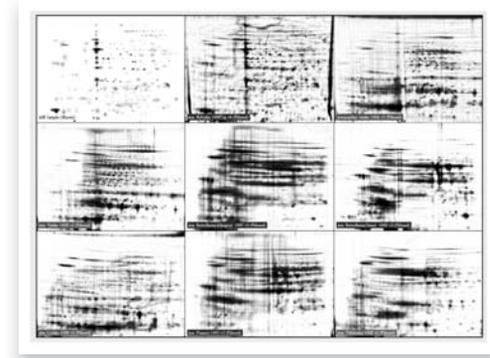


Figure 3: 2-D Gel images from each of the different *Amaranthus* samples are shown here. An average total number of 447 spots were resolved and the spots were matched between all the gels. Obvious qualitative similarities and differences are seen.

Gel Name	Resolved Spots
<i>A. hybridus</i> 149F	308
<i>A. viridis</i> 149A	557
<i>A. viridis</i> 149H	550
<i>A. retroflexus</i> (Allergon) 149C	361
<i>A. retroflexus</i> (Greer) 149D	376
<i>A. lividus</i> 149B	609
<i>A. plameri</i> 149G	415
<i>A. tuberculatus</i> 149E	407

Table 1: The number of resolved spots as presented in Figure 3.

Project Title: An Environmental, Epidemiological and Clinical Investigation of Allergy and Asthma in Relation to Outdoor and Indoor Aeroallergens in the Holy Cities of Saudi Arabia, RAC #2081 121 (KACST #ARP 29-134).

Investigators: Syed M. Hasnain, PhD, FACAAl, FAAAAI, Abdulkareem Ayodele Alaiya, MBBS, MPH, PhD, Mohammad Osman Gad-el-Rab, MD, Yasmin Al Tuwajjri, PhD

PROJECT DESCRIPTION

- To conduct qualitative and quantitative investigation of environmental (outdoor/indoor) aeroallergens in the two populated Holy cities. (Makkah Al Mokarramah, and Madin Al Manuwwarah) using state –of –the art Sampling technique, collection and immunoassays such as Burkard Volumetric trap for outdoor and MARIA or ELISA for indoor.
- To evaluate and enumerate their clinically significant and threshold levels, frequency, seasonal and diurnal periodicities, maximum concentrations and relationship to bronchial asthma and other allergic manifestations.
- To conduct epidemiological studies of bronchial asthma and allergic rhinitis in schoolchildren in the two cities.
- To conduct *in vivo* and *in vitro* investigative test on allergic and asthmatic school children to evaluate the allergenicity of the citizens and the reactivity of the recognized indigenous inhalants in the two regions.
- To compare and relate the prevalence studies with the previous studies in the kingdom.
- To compare and relate the aeroallergens profiles with asthma and allergic rhinitis in the Holy sites and with available similar data from other cities in Saudi Arabia.

PROGRESS

To be continued.

ALLERGOTEK PROGRAM

Allergotek Diagnostic and Therapeutic Program; After the successful clinical trial of our kits we are in the process of collecting forty-five different types of pollen, fungal spores and miscellaneous inhalants with quality control and molecular fingerprinting for each sample.

- A preliminary webpage for Allergotek, with the help of Ms. Shazia N. Subhani of BESC Department, was completed. The site will be further reviewed and revised at an appropriate time coinciding with the launching of the Allegotek products.
- Mr. Francisco Marañon Lizana (a specialist in industrial pollen collection from Madrid (Spain)

visited for separation purification of high yield pollen grains.

WORLD ASTHMA DAY

The unit celebrated the World Asthma Day on 7th May 2008 under the theme “*You can control your Asthma by: protection and prevention*”. The awareness day was at Al-Mather Park at KFSHRC compound.

To give the public a close look at the allergens in the environment and for more knowledge about airborne allergens, a show and demonstration of allergens were organized.

- Display and explanation of House Dust mite, types, photos, viewing the mite under microscope and how to control the House Dust Mite.
- Display and explanation of the most common airborne allergenic pollen grains in the kingdom, viewing anthers and pollens under microscope.
- Display and explanation of some of the most common allergenic fungi in the air, viewing some in cultures and in microscopic vision.
- Demonstration of air sampling (collection of samples from the air) using air samplers.
- Show of different types of most common allergic plants found in Saudi Arabia. (Herbarium and fresh plants).

IN ADDITION THE FOLLOWING SEMINARS/ LECTURES WERE PRESENTED

- A lecture by Dr. Abdurrahman Al-Frayh, Chairman of the National Asthma committee in KSA. Ex –dean of College of Medicine at King Saud University. Riyadh.
- A lecture by Dr. Syed Hasnain, Head of Allergy and Aerobiology unit, BMR. King Faisal Specialist Hospital and Research Centre, Riyadh.
- Open panel discussion with participation of Dr. Bandar ibn Khalid along with the medical team.
- Announcement of the winners and prizes distribution. Hundreds of schoolchildren along with their families gathered to attend the awareness

programs on causes and prevention of allergic diseases. It was a successful awareness day.

APAWG (ASIA PACIFIC AEROALLERGEN WORKING GROUP)

The head of the unit (Syed M. Hasnain, PhD) was appointed by the WAO (World Allergy Organization), as the Editor for the Asia Pacific Aerollerger Working Group news letter. The newsletter has been posted on the WAO website, which will be accessible to members in 77 countries. The newsletter provides information about upcoming regional and international events and projects as well as past work. It also offers a publication list, featured review article and links to a variety of key resources including APAWG's publications: *Aeroallergen Monitoring Standard for the Asia Pacific Region*.

ASTHMA EDUCATIONAL COMMITTEE (AEC)

The Asthma and educational committee of the hospital formally appointed the unit head (Syed M. Hasnain, PhD) as a member of the committee. The unit will celebrate the World Asthma Day jointly with AEC for the year 2009.

FUTURE RESEARCH DIRECTION

The unit 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. Our activities will continue in all the afore-mention areas to achieve our goals and objectives.

ACKNOWLEDGEMENT

The laboratory staff would like to express their thanks and appreciations to the support facilities at the RC, particularly Mr. Hakem Al-Enazi, Manager,

Logistics and Facility Services, Computer Core Facility (Mr. Parvez Siddiqi and Mr. Yousef Hussain), and the secretarial staff of the administration.

FURTHER STATISTICAL ANALYSIS

The statistical analysis of various allergens tested under clinical trial project no. RAC 2060 006 were completed with the help of Mr. Saleh Al-Ghain (BESC Department). Correlations are being summarized for publication.

PUBLICATIONS

- ↪ HASNAIN, SM, KHAN, M, SALEEM, A, WAQAR, MA: (2008) "Prevalence of Asthma and Allergic Rhinitis among School children of Karachi, Pakistan, 2007". *Journal of Asthma and Allergy*. Volume 46, Pages 86-90, 2009.
- ↪ WAQAR, MA, KHAN, M, HASNAIN, SM, ET AL. "Prevalence of Allergy and Asthma in School of Islamabad, Pakistan". *World Applied Sciences Journal* 6 (3): 426-432, 2009.
- ↪ WAQAR, MA, KHAN, M, SALEEM, A, HASNAIN, SM.: "Pollen allergy: The effects of cultivated plants on sensitive patients in the province of Sindh, Pakistan". (Accepted).
- ↪ HASNAIN, SM. KHATJJA, F, AL-FRAYH, AR, KOSHAK, E. "An Outdoor Aeroallergen Calendar of Saudi Arabia, Dammam, Qassim, Jeddah and Riyadh". *Saudi Medical Journal*. (Accepted)
- ↪ KHAN, M, WAQAR, MA, HASNAIN, SM: "An updated study of airborne pollen grains in Karachi city by Burkard's 7-day Volumetric Spore Trap". (Submitted to *Aerobiologia*).

INVITED LECTURES

- ↪ Invited speaker: The cause of allergies and Asthma. Video-conference lecture nation-wide, Dr Panjwani centre for Molecular Medicine and Drug Development, ICCBS, University of Karachi, Pakistan, 23 Feb, 2008.

- ↪ Invited speaker: The prevention and control of Allergies and Asthma. Video Conference lecture nation-wide, Dr Panjwani centre for Molecular Medicine and Drug Development, ICCBS, University of Karachi, Pakistan, 26 Feb, 2008.
- ↪ Invited speaker: Clinically Relevant Respiratory Allergens in Saudi Arabia; Staloral launch by Stallergen, Conrad Hotel, Cairo, 29-31 May, 2008.
- ↪ "Role of allergens in allergy", World Asthma Day 2008 – Awareness Day, Al-Mather Cave Park, King Faisal Specialist Hospital and Research Centre. 08 May 2008. (Organized event)
- ↪ Invited speaker: Medical Grand Rounds "Saudi Allergens for Diagnosis and Immunotherapy of Allergic Diseases". Postgraduate Center Auditorium, King Faisal Specialist Hospital and Research Centre.

PRESENTATION AND CONFERENCES

- ↪ HASNAIN, SM, ALAIYA, AA, GAD-EL-RAB, MO, ET AL. *Amaranthus* Pollen Extracts: Protein Diversity and

Impact on Diagnosis. *Journal of Allergy and Clinical Immunology*, Volume 123, Issue 2, Pages S160-S160. 2009.

- ↪ KHAN M, HASNAIN SM, WAQAR MA: Allergy and Asthma in Pakistan: "Airborne Pollen Prevalence in City of Karachi, Pakistan" Dr. Panjwani Centre for Molecular Medicine and Drug Research (PCMD), University of Karachi. (Poster presentation).

TECHNICAL REPORT TO KACST

- ↪ A Technical Report to KACST – Project ARP 27-11. Isolation, Purification and Immunochemical Characterization of Allergic Protein(s) from *Amaranthus viridis* Pollen Grains. (12 pages)
- ↪ Annual Progress Report for the First Year – Project ARP 27-11. Isolation, Purification and Immunochemical Characterization of Allergenic Protein(s) from *Amaranthus viridis* Pollen Grains. (79 pages)

Breast Cancer

Breast 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 hence 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 of Unit:

Suad Bint Mohammed Bin Amer, PhD

Members:

Asma Nofal

Gina Gonzalez

RESEARCH PROJECTS

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

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

PROGRESS

Sample Collection

Collection of freshly resected Breast tumor and tumor adjacent tissues samples is continued in collaboration with clinicians and pathologists by using the internationally standardized protocol.

Gene Expression Analysis

We analyzed the whole-genome mRNA expression profile from tumor and adjacent disease free tissues of 115 samples using Affymetrix GeneChip Human Genome U133 Plus 2.0 Arrays. Both unsupervised and supervised analyses were performed. We have found 1756 genes as differentially expressed between patients compared to normal controls (adjusted p value < 0.05 and fold change > 2). The hierarchical clustering as well as principle component analysis (PCA) clearly separated individuals as either patients or normal controls. We have identified age-specific tumor signature genes for very young age (age < 35) and two mature groups. Functional and pathway analysis revealed some distinct and shared functional categories and pathways among three age subgroups. Our initial results on cancer progression revealed that there are most changes occur between normal to IDC, with relatively smaller list of differentially expressed genes distinguishing DCIS from normal. Further investigation of this list is warranted because it potentially contains the key genes as well as the pathways that they are involved and are important in the transformation from DCIS to IDC breast cancer. Moreover, breast cancer appearing in young women share unique biological characteristics that should be highlighted and applied in diagnosis and prevention. We hope that our result will contribute immensely in the therapy management of our patients.

Project Title: Determination of the Role of Several Radio-Fluorinated Bombesin Peptides as Molecular Imaging Agent for the Detection of Breast Cancer (RAC # 2030058). In collaboration With Department of Cyclotron.

Investigators: Suad Bint Mohamed Bin Amer and Ibrahim Al-Jamaz

PROJECT DESCRIPTION

Breast Cancer cell lines are being established and maintained in order to determine the role of several radio-

fluorinated Bombesin peptides as a molecular imaging agent for the detection of Breast Cancer.

FUTURE RESEARCH DIRECTION

- Functional and pathway analysis of the signature genes identified for the very young aged breast cancer patients (age 20-35) will be performed. Selected genes from the signature genes will be validated using realtime RT-PCR and immunohistochemistry.
- We will also compare the gene expression profile of our Saudi breast cancer patients of young group (age <45) with older group (age >45; which will be further divided in to two groups: peri-menopause and post-menopause). After identifying the signature genes, we will compare it with the microarray gene expression data, which will be obtained from public databases, for breast cancer patients in the West (Europe and/or USA) to identify ethnic differences and similarities in the molecular level among breast cancer patients.
- A major challenge to human breast cancer research has been the characterization of the molecular events that are taking place during the cancer progression. We would like to examine in more detail the gene expression signatures characteristic to the sequential disease stages (DCIS, and IDC) of our Saudi breast cancer patients, and to identify a subset of genes with quantitative expression levels that correlate with advanced tumor grade and with the transition from DCIS to IDC.

Carcinogenesis

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 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 of 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 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 of Unit:

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.

PROGRESS

The final report was submitted to the KACST.

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, 17b-Triol
4. 1, 3, 5 (10)-Estratrein-2, 3-Diol-17-one
5. 1, 3, 5(10)-Estratrien-3, 17b-Diol

The above 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

SUMMARY

Our results showed that estradiol and its metabolites (2-hydroxyestrone and 2-hydroxy-17 β -estradiol) were quite effective in inducing the cytotoxicity and apoptosis in all the cancer cell lines. The 2-hydroxy-17 β -estradiol and 2-hydroxyestrone were inducing up to 85% apoptosis in breast (MCF-7 and MDA-MB-231), uterine (HEC-1A) and ovarian (OVCAR-3) cancer cell lines killing almost all the cells at 72 h time point. 17 β -Estradiol was relatively less effective. The most significant and unexpected results were with the equine estrogens (equilin and equilenin) which showed neither apoptosis nor cytotoxicity in any of the cancer cell lines as opposed to our hypothesis. The estrogen receptors (ER) seem to have played a role in eliciting the response by estradiol and its metabolites. The ER- β negative MDA-MB-231 cells showed least effect with estradiol but on the other hand the metabolites showed relatively better response. Further, the structure-activity relationship might also be playing a role in differential cytotoxic response of these estrogens.

PUBLICATIONS

- 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*, (2008)17:297-304.

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, present in 42% of the adult male and 37% of the adult female Saudi population. Our Diabetes Program consists of seven main projects: [1] RAC 22060 007: Diet-induced Metabolic Syndrome and Type 2 Diabetes in a rodent model. [2] RAC 2070 006 in vitro metabolic studies into the etiology of Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Hepatic Steatosis (NASH) in hepatocytes. [3] RAC 2060 037: Type 2 Diabetes and cognitive dysfunction in a feline model. [4] RAC 2061 027: 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] RAC 2050 046: Lentiviral Gene delivery of the anti-inflammatory agent Vaccinia Virus Complement Protein (VCP) in a small-animal model. [6] RAC2000 002. 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.

Head of Unit:

Futwan A Al-Mohanna, PhD, FIBiol, FRSC

Members:

Zakia Maqbool, PhD

Mohammed Al-Johi, PhD

Soad Saleh

Angela Inglis

Nadine Makhool

Razan Bakheet

Reem Al-Hejailian

Rana Al-Rabiah

Marya Zia

Rhea Mondreal

Mohammed Al-Halaby

RESEARCH PROJECTS/ACTIVITIES

Project Title: Metabolic Syndrome, Diabetes and Cognitive Decline: Effect of Dietary Components on Insulin Resistance, Hyperlipidemia, Inflammation and Cognition in a Rodent Model, RAC#2060 007.

Investigators: Collison, K; Saleh, S; Inglis, A; Bakheet, R; Al-Johi, M; Shoukri, M & 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 2 full-length publications accepted and 1 presentation at the 2nd World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension meeting, Barcelona, Spain.

Project Title: 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, RAC# 2061027.

Investigators: Collison, K; Subhani SN; 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

Over 8000 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. Manuscript in preparation.

Project Title: Metabolic Studies into the Etiology of Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Hepatic Steatosis (NASH).

Investigators: Collison, K; Saleh, S; Al-Mohanna, F.

PROJECT DESCRIPTION

Nonalcoholic fatty liver disease is a new and increasingly prevalent metabolic disease of the industrialized world. We hypothesized that increased consumption of dietary fructose in the form of high fructose corn syrup (HFCS) might contribute to the pathogenesis of nonalcoholic fatty liver disease. We set out to test this both *in vitro*, using tissue culture cells, and *in vivo*, using a rodent model.

PROGRESS

Exposure of hepatocytes to HFCS-55 caused a significant increase in hepatocellular triglyceride and lipogenic proteins. Basal production of reactive oxygen metabolite (ROM) was increased, together with a decreased capacity to respond to an oxidative challenge. HFCS-55 induced a down-regulation of the insulin signaling pathway, as indicated by attenuated ser473 phosphorylation of AKT-1. JNK, which is intimately linked to insulin resistance, was also activated; and this was accompanied by an increase in endoplasmic reticulum stress and intracellular free calcium perturbation. Hepatocytes exposed to HFCS-55 exhibited mitochondrial dysfunction and released cytochrome C into the cytosol. Hepatic steatosis and mitochondrial disruption was induced *in vivo* by a diet enriched with 20% HFCS-55; accompanied by hypoalbuminemia and elevated fasting serum insulin and RBP4 levels. Publication accepted.

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

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

PROJECT DESCRIPTION

Feline diabetes closely resembles human type 2 diabetes. Symptoms of the metabolic syndrome and markers of insulin resistance were induced in test subjects using specific dietary manipulation of animals bred from female cats consuming the tested diets. Cognitive studies were performed towards the end of the study to assess working spatial learning and memory.

PROGRESS

All data and samples have been collected, and we are in the process of analyzing it.

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 used the lentiviral Gene Delivery System to ascertain the anti-inflammatory effects of VCP *in vitro* and *in vivo*.

PROGRESS

The Lentiviral constructs have been completed. Viral Titres were made.

Project Title: Oxford Heart Project: Reversible Model of Ovine Heart Failure, RAC#2000 002.

Investigators: Quittaineh, M; Collison, K; Saleh S and Al-Mohanna, FA

PROJECT DESCRIPTION

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

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

- ↪ Collison KS, Maqbool Z, Saleh SM, Inglis A, Makhoul NJ, Bakheet R, Al-Johi M, Al-Rabiah R, Zaidi MZ, Al-Mohanna FA. Effect of dietary monosodium glutamate on trans fat-induced nonalcoholic fatty liver disease. *J Lipid Res.* 2008 Nov 11. [Epub ahead of print].
- ↪ Collison KS, Saleh SM, Bakheet RH, Al-Rabiah RK, Inglis AL, Makhoul NJ, Maqbool ZM, Zaidi MZ, Al-Johi MA, Al-Mohanna FA. Diabetes of the Liver: The Link Between Nonalcoholic Fatty Liver Disease and HFCS-55. *Obesity* (Silver Spring). 2009 Mar 12. [Epub ahead of print].
- ↪ Amartey JK, Shi Y, Al-Jammaz I, Esguerra C, Al-Otaibi B, Al-Mohanna F. Radioiodinated naphthylalanine derivatives targeting pancreatic beta cells in normal and nonobese diabetic mice. *Exp Diabetes Res.* 2008; 371716.
- ↪ Baitei EY, Zou M, Al-Mohanna F, Collison K, Alzahrani AS, Farid NR, Meyer B, Shi Y. Aberrant BRAF splicing as an alternative mechanism for oncogenic B-Raf activation in thyroid carcinoma. *J Pathol.* 2009 Apr; 217(5):707-15.
- ↪ Shi Y, Zou M, Baitei EY, Alzahrani AS, Parhar RS, Al-Makhalafi Z, Al-Mohanna FA. Cannabinoid 2 receptor induction by IL-12 and its potential as a therapeutic target for the treatment of anaplastic thyroid carcinoma. *Cancer Gene Ther.* 2008 Feb;15(2):101-7. Epub 2007 Dec 21.
- ↪ Al-Ahmadi W, Al-Haj L, Al-Mohanna FA, Silverman RH, Khabar KS. RNase L downmodulation of the RNA-binding protein, HuR, and cellular growth. *Oncogene.* 2009 Mar 2. [Epub ahead of print].
- ↪ Alazami AM, Al-Saif A, Al-Semari A, Bohlega S, Zlitni S, Alzahrani F, Bavi P, Kaya N, Colak D, Khalak H, Baltus A, Peterlin B, Danda S, Bhatia KP, Schneider SA, Sakati N, Walsh CA, Al-Mohanna F, Meyer B, Alkuraya FS. Mutations in C2orf37, encoding a nucleolar protein, cause hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal syndrome. *Am J Hum Genet.* 2008 December; 83(6):684-91. Epub 2008 November 20.

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 found that curcumin is an enhancer of the killing effect of the anti-medulloblastoma agent cyclopamine.
- We have also demonstrated that the Atr protein kinase is a major regulator of the cellular response to UV damage and protects cells from UV-induced apoptosis.
- The majority of breast cancer stromal fibroblasts express low levels of the tumor suppressor Atr protein.

Head of Unit:

Abdelillah Aboussekhra, PhD

Members:

Nisreen M. Al-Moghrabi, PhD

Bedri Karakas, PhD

Siti Faujiah Hendrayani, MSc

Ibtehaj S. Al-Sharif, BSc

Nujoud Al-Yousef, BSc

RESEARCH PROJECTS

ProjectTitle: 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.

PROGRESS

We have shown that curcumin and cyclopamine (an inhibitor of the Sonic Hedgehog signaling pathway) have synergistic effect in inducing apoptosis in resistant medulloblastoma cells. Figure 1 shows that while the effect of the single agents (curcumin or cyclopamine) is only marginal the combination of curcumin and cyclopamine triggered high proportion of apoptotic cells. Indeed, more than 80% of medulloblastoma cells died through apoptosis when cyclopamine (20 μ M) was added to curcumin (20 μ M). This shows that curcumin potentiates the anti-medulloblastoma effect of cyclopamine by enhancing its inhibitory effect on the Hedgehog signaling pathway.

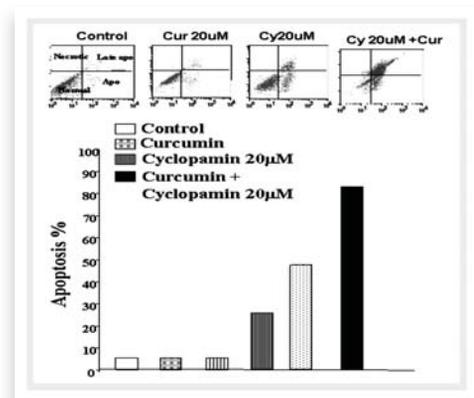


Figure 1: Curcumin potentiates the effect of cyclopamine in inducing apoptosis in medulloblastoma cells. AnnexinV/PI-Flow cytometry.

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 oncoproteins in both tumor cells and their associated fibroblasts.

PROGRESS

ATR expression is down-regulated in most breast cancer stromal fibroblasts (CAFs).

The basal expression level of the Atr protein was assessed in 10 CAFs and their adjacent normal counterparts from normal tissues (TCFs). Whole cell extracts were prepared and 30 μ g proteins were used for western blot analysis using a specific antibody and GAPDH as internal control. Interestingly, in 7 cases

out of 10 (70%) the level of Atr was significantly lower in CAFs than in their adjacent counterparts (TCFs). In the 3 other cases similar level of Atr has been observed (Figure 2). This indicates that the down-regulation of Atr in stromal fibroblast could play a major role in breast carcinogenesis and especially the relationship between epithelial cells and their microenvironment.

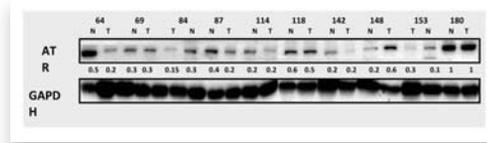


Figure 2: ATR expression is low in breast cancer associated fibroblasts. Western blot showing the expression of the Atr protein kinase in stromal fibroblasts from tissues extracted from different patients. N: TCF, T: CAF.

FUTURE RESEARCH DIRECTION

Further characterize the curcumin as potential potent anti-cancer drug. Elucidate the role of the Atr protein kinase in the interaction between breast stromal fibroblasts and breast cancer cells. We are also interested in studying the role of other tumor suppressor proteins in this process. Furthermore, we would like to determine

non-toxic agents with the ability to normalize the stromal fibroblasts and their effects on epithelial cells.

PUBLICATIONS

- ↪ Nahed M. Hawsawi, Hazem Ghebeh, Siti-Faujiah Hendrayani, Asma Tulbah, Maha Al-Eid, Taher Al-Tweigeri, Dahish Ajarim, Ayodele Alaiya, Said Dermime and Abdelilah Aboussekhra. Breast carcinoma-associated fibroblasts and their counterparts display neoplastic-specific changes. (2008). *Cancer Res.*, 8: 2717-2725.
- ↪ 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*, 87:123-132.

Environmental Health

The Environmental Health Section (EHS) studies the impact of various pollutants such as heavy metals, pesticides and polycyclic aromatic hydrocarbons; with special emphasis on the Saudi environment and public health. Last year, we managed to start our newly funded project by King Abdulaziz City for Science and Technology. Meanwhile, we continue to offer opportunities for both in-house and postgraduate training and collaborations with local academic institutions. This report describes the progress of our ongoing projects, identifying 2007-2008 significant accomplishments and anticipated future directions.

Head of Unit:

Iman Al-Saleh, PhD

Members:

Neptune Shinwari

Abdullah Mashhour

Ammar Al-Sabbahen

Sami Al Enazi

Reem Al-Rouqi

Al Anoud Al-Sedairi

RESEARCH PROJECTS/ACTIVITIES

ONGOING RESEARCH PROJECTS

Project Title: "Effects of Environmental Pollutants Exposure on the Pregnancy Outcome of Women in Al-Kharj Area", RAC # 2040 017.

Principal Investigator: Iman Al-Saleh

Co-Investigators: Mohamed Hassan Gamal El Din and Abdulla Rabah

This project is funded by King Abdulaziz City for Science and Technology (KACST # AT 23-7) for a total of SR 393,600. The project was started on 7th July 2005 in collaboration with King Khalid Hospital, Al-Kharj for a period of 48 months.

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. It should be noted that there have a number of hospital-based studies in different cities in Saudi Arabia, which reported a high prevalence of birth defects, infant mortality and congenital malformations. 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 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

1. The completion of hydroxypyrene in 1578 urine samples;
2. The completion of 8-hydroxy-2-deoxyguanosine in 790 urine samples; &
3. The completion of lead, cadmium and mercury in 1578 placental tissues;
4. The completion of *p,p*-DDT and its metabolites (*p,p*-DDE and *p,p*-DDD) analysis in 1578 placental tissues; &

5. The project was extended by King Abdulaziz City for Science & Technology for another year.

PRELIMINARY RESULTS ON METAL ANALYSIS

The mean maternal blood lead at delivery was $2.897 + 1.851 \mu\text{g/dL}$, with a range of $0.073\text{-}25.955 \mu\text{g/dL}$; and the mean cord lead was $2.551 + 2.592 \mu\text{g/dL}$, with a range of $0.154\text{-}56.511 \mu\text{g/dL}$. Average maternal lead levels were significantly higher than the average lead levels in cord blood ($t=-9.52$, $P=0$). Lead was detected in all maternal and cord blood samples. Only 7 mother and 6 newborns had lead levels less than the detection limit for lead ($0.4\mu\text{g/dL}$). Among subjects in the present analysis, 14 mothers (0.89%) and 13 newborns (0.83%) had blood lead levels above the United States Center for Disease Control (CDC) allowable threshold limit of $10 \mu\text{g/dL}$ blood lead.

Similarly, cadmium was detected in all samples with approximately 94.8% and 97.9% of cord and maternal blood samples above the detection limit of cadmium ($0.42\mu\text{g/L}$). The estimates of cord and maternal cadmium levels averaged $0.78 + 0.623\mu\text{g/L}$ (range= $0.245\text{-}15.525\mu\text{g/L}$) and $0.986 + 0.313\mu\text{g/L}$ (range= $0.233\text{-}3.157\mu\text{g/L}$) respectively. Cadmium levels were significantly higher in maternal blood than in cord ($t=-21.42$, $P=0$). While 5 newborns had blood cadmium levels $>5 \mu\text{g/L}$, the OSHA Safety Standard for cadmium (OSHA 2003), none was detected in maternal blood. On the hand, there were 204 newborns (13%) and 761 women (48.6%) who had cadmium $> 1\mu\text{g/L}$ (the threshold limit of clinical importance).

The maternal mercury blood levels ranged from $0\text{-}206.41 \mu\text{g/L}$ with a mean value of $3.005 + 6.319 \mu\text{g/L}$. The corresponding levels of their newborns ranged from $0\text{-}26.532 \mu\text{g/L}$ with a mean of $3.354 + 2.673 \mu\text{g/L}$. In 96 newborns (6.1%) and 196 mothers (12.5%), mercury levels were less than DL of $0.25\mu\text{g/L}$. Unlike lead and cadmium, mercury in cord blood was significantly higher than in maternal blood with t -value of 8.036 ($P=0$). Our study showed that 203 newborns (13%) and 176 mothers

(11.2%) had mercury concentrations greater than the EPA reference dose of $5.8 \mu\text{g/L}$ (CDC 2004; US EPA, 2007).

Project Title: "Saudi Children and mercury exposure: the impact of dental amalgam", RAC# 2070 010.

Principal Investigator: Iman Al-Saleh

Co-Investigators: Al Anoud Al-Sudairi and Ebtesam Al Olyan

This is a master research project in collaboration with the Department of Zoology, King Saud University. The project was started on 2nd June 2007 for a period of one year.

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

Last year, we worked hard to complete sample analyses. Mercury in urine, hair and nail samples were determined. All the proposed biomarkers in this project were completed including N-acetyl- β -d-glucosaminidase, α_1 -microglobulin, β_2 -microglobulin and 8-hydroxy-2-deoxyguanosine in urine samples. We are presently in the process of compiling the data and making our final conclusions.

NEWLY APPROVED PROJECTS

Project Title: "Determination of Phthalates in Drinking Water, Juices and Milk Packed in Locally Manufactured Plastic Bottles, RAC # 206 0028.

Investigators: Iman Al-Saleh.

This project is funded by King Abdulaziz City for Science and Technology (KACST # LGP-12-7) with a total fund of SR 75,000. The project was started on 2nd July 2008 for duration of one year.

PROJECT DESCRIPTION

Phthalates are small, fat-soluble chemicals found in polyvinyl chloride (PVC) products which are used to soften vinyl plastic. They are animal carcinogens which can cause fetal death, malformations, and reproductive toxicity in laboratory animals. The overall aim of this project, is to analyze ten widely consumed brands of bottled milk, juices and drinking water samples manufactured locally and collected from various stores in Riyadh for five of the most widely used phthalates as plasticizers in PVC that are regularly assessed by the EU to determine whether they pose any risk to human health or the environment. These are di-(2-ethylhexyl) phthalate (DEHP), di-butyl phthalate (DBP), di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP) and benzyl butyl phthalate (BBP). Moreover, the effect of temperature and duration of storage on the levels of these phthalates in drinking water will be investigated.

PROGRESS

Since the start of the project, we have managed to develop the method for measuring phthalates in juices using the Gas Chromatography with Electron Capture Detector-GC/ECD. Chromatography with Mass Spectrometer (GC/MS) was also used to confirm its presence in juices.

CORE SERVICE ACTIVITIES

SERVICE-FOR-FEE ACTIVITIES

1. Analysis of lead, cadmium, mercury, arsenic,

antimony, nickel and chromium in cosmetics samples for the Saudi Food & Drug Authorities.

2. Analysis of mercury and hydroquinone in skin-lightening creams for the Saudi Food & Drug Authorities.

FUTURE RESEARCH DIRECTION

The EHS will continue to study the health impact of the changing Saudi environment and explore new area of interdisciplinary research. Our ultimate aim is to transfer a knowledge base that can be utilized for scientific analysis, environmental reforms, professional training and public awareness.

PUBLICATIONS

- ↪ Al-Saleh I, Arif J, El-Doush I, Al-Sanea N, Abdul Jabbar A, Billedo B, Shinwari N, Mashhour A, Mohamed G. Carcinogen-DNA adducts and the risk of colon cancer: Case-control study. *Biomarkers* 2008; 13: 201-216.
- ↪ 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* 2008; 211: 560-579.
- ↪ Al-Johar D, Shinwari N, Arif J, Al-Sanea N, Abdul Jabbar A, El-Sayed R, Mashhour A, Billedo G, El-Doush I, Al-Saleh I. The role of *Nigella sativa* and a number of its antioxidant constituents towards azoxymethane-induced genotoxic effects and colon cancer in rats. *Phytotherapy Research* 2008; 22(10):1311-1323.
- ↪ Al-Saleh I, Shinwari N, Mashhour A, Nester M, Moncari L, Rabah A, Mohamed G. Longitudinal study of prenatal and postnatal lead exposure and early cognitive development in Al-Kharj, Saudi Arabia: A preliminary results of cord blood lead levels. *Journal of Tropical Pediatrics* 2008; 54(5): 300-307.

Laser Medicine

Low 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.

Head of Unit:

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

BREAKTHROUGH

LASER THERAPY CONVERTS DIABETIC WOUND AND BURN HEALING TO NORMAL HEALING.

Photomedicine & Laser Surgery, Vol. 27, No. 1, 2009 , Pp. 127-135 (RAC # 2020 002).

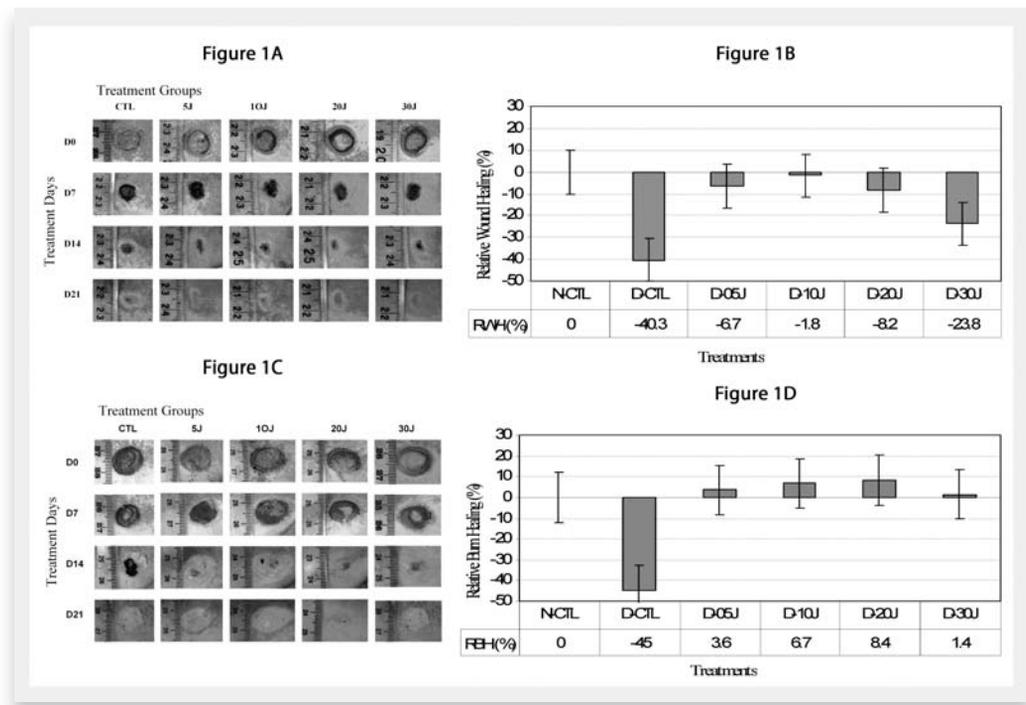


Figure 1A & 1B: 633 nm Laser Therapy of Diabetic Oval Full-Thickness wound.

Figure 1C & 1D: Laser Therapy of Diabetic Burn

RESEARCH PROJECTS

Project Title: Photo-Biostimulation: Laser Effect in Wound Healing of Diabetic and Non Diabetic Rats, RAC #2020 002.

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), CO₂ (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: Laser Biostimulation: Wound Healing, RAC# 960002.

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 bio-modulation 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.

Project Title: Photodynamic Therapy on Nude Mice Using Different Tumors and Photosensitive Drugs, RAC# 2080 044.

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

PROJECT DESCRIPTION

Photodynamic therapy (PDT) is increasingly being recognized as an attractive, alternative treatment modality for malignant disease. The study is to evaluate and compare the effects of PDT using photosensitizers of Porfimer sodium, Amino levulinic acid (5-ALA), and meso-tetra-hydroxyphenyl-chlorin (mTHPC) for treating human undifferentiated thyroid carcinoma (UTC), Murine fibrosarcoma (RIF-1) and Mammary adenoma (EMT-6) on male nude mice. Undifferentiated thyroid carcinoma (UTC), Murine fibrosarcoma (RIF-1) and Mammary adenoma (EMT-6) will be inoculated in the right flank of the mice. When tumor volumes reach about 300 mm³, all mice will be divided randomly into treatment group and control group. Three kinds of photosensitive drugs will be used: Porfimer sodium,

(Photofrin[®]), ALA (Levulan[®]) and mTHPC (Foscan[®]). The tumors will be irradiated by a diode laser with 633 nm or 652 nm wavelength. The mice in control group will also receive the same manipulation, excluding the application of photosensitive drug and irradiation of laser light. The tumor volumes will be determined by a caliper (Scienceware) on day zero (start day of PDT), 7th day, 14th day and 21st day after PDT in treated and control groups. The % of tumor growth delay after PDT will be calculated. All mice will be sacrificed by the dislocation of cervical vertebra and the tumors extirpated on the 21st day after PDT. The tumor weight will be determined by a scale (Voyager) in all animals. Statistical analyses will be performed using the student's t test for comparison of data between control and treated groups. Differences are considered statistically significant when the p value was < 0.05.

SPECIFIC AIMS

The aim of the study is to evaluate and compare the effects of photodynamic therapy using photosensitizers of Porfimer sodium (Photofrin), Amino levulinic acid (5-ALA), and meso-tetra-hydroxyphenyl-chlorin (mTHPC) for treating human undifferentiated thyroid carcinoma (UTC), Murine fibrosarcoma (RIF-1) and Mammary adenoma (EMT-6) on nude mice.

PROGRESS

Project proposal was submitted in November 2008 and waiting for ORA approval to proceed with experiments.

FUTURE RESEARCH DIRECTION

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 21st 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. Accordingly, the laser continues to be an important tool in clinical patient care in this 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

BOOK CHAPTER

- ↔ F.A.H. Al-Watban, B.L. Andres, X.Y. Zhang, A.A. Al-Anazi (Book Chapter 2008) "PHOTOBIOSTIMULATION: The Effect of Various Lasers in Non-Diabetic and Diabetic Wound and Burns" in *Laser Medicine, Dentistry, Surgery and Veterinary 4th Book*, Zlatko Simunovic et. al. eds. (in-press).

FULL MANUSCRIPTS

- ↔ F. A.H. Al-Watban, B. L. Andres (Paper 2008). "Low Power Laser Therapy for Wound and Burn Healing", *Arab Health 2008*, Issue 3, Pp.48-51.
- ↔ F.A.H. Al-Watban, , X.Y Zhang, B.L. Andres, A.A. Al-Anazi (Paper 2008). "Visible Lasers Were Better Than Invisible Lasers in Acceleration Burn Healing on Diabetic Rats" *Photomedicine & Laser Surgery*, Vol. 26, No. 5, 2008, pp. 00-00 (advanced electronic publication).
- ↔ F. A.H. Al-Watban (Paper 2009). "Laser Therapy Converts Diabetic Healing to Normal Healing" *Photomedicine & Laser Surgery*, Vol. 27, No. 1, 2009, Pp. 127-135.

ABSTRACTS

- ↪ F.A.H. Al-Watban, B.L. Andres, X.Y Zhang, A. A. Al-Anazi (Abstract 2008). "Modification of Scar Tissue Morphology Using Low Power Diode Laser (670 Nm) On Burn Healing", Proceedings of NZLASER 2008, Laser Therapy and Phototherapy From New Zealand to the World, 26-27 April 2008 at Queenstown, New Zealand.
- ↪ F.A.H. Al-Watban,, X.Y Zhang, B.L. Andres, A.A. Al-Anazi (Abstract 2008). "Cosmetic Effect of Low Power Diode Laser (670 Nm) Light On The Healing of Burns", Proceedings of the 3rd International Congress on Anti-Aging Medicine & 1st International Congress on Lasers In Medicine and Surgery 2-4 May 2008 at Bucharest, Romania.
- ↪ F.A.H. Al-Watban, X.Y Zhang, B.L. Andres, A.A. Al-Anazi (Abstract 2008). "The Application of Low Power Laser in Accelerating Wound & Burn Healing on diabetic Rats", Laser Helsinki 2008 13th International Congress of EMLA (European Medical Laser Association), in conjunction with EMLA Finland and MAL in cooperation with ASLMS, 23-24 August 2008, Helsinki, Finland.
- ↪ XingYang Zhang, F.A.H. Al-Watban, B.L. Andres (Abstract 2008). "The Changes of Tumor Volume and Weight after PDT: An Animal Study", 7th International congress of World association for Laser therapy (WALT 2008), 19-22 October 2008, Sun City, South Africa.
- ↪ B.L. Andres, F.A.H. Al-Watban, XingYang Zhang (Abstract 2008). "Comparison of 633nm Diode Laser Therapy, Regranex and Solcoseryl in Diabetic Burn Healing: Biochemical and Biomechanical Analysis of Scar", 7th International Congress of World Association for Laser Therapy (WALT 2008), 19-22 October 2008, Sun City, South Africa.
- ↪ F.A.H. Al-Watban, X.Y. Zhang, B.L. Andres, A.A. Al-Anazi (Abstract 2008). "The Significance of Treatment Parameters Using Various Photon sources in Normal and Diabetic Wound and Burn Healing", 7th International Congress of World Association for Laser Therapy (WALT 2008) 19-22 October 2008, Sun City, South Africa.
- ↪ F. A.H. Al-Watban (Abstract 2008). "Laser Science and Technology in Biomedicine for the Arab World",

Proceedings for 5th Congress of Scientific Research Outlook in the Arab World-Scientific Innovation and Sustained Development, 26-30 October 2008, Fez, Morocco.

- ↪ F.A.H. Al-Watban, B. L. Andres, X.Y. Zhang (Abstract 2008). "The Effect Of LPL Therapy On The Cosmetics Of Burn And Wound Healing In Diabetic Rats", Dubai Congress on anti-Aging Medicine (DCAAAM), 7-9 November 2008, Dubai, UAE.
- ↪ F.A.H. Al-Watban, B.L. Andres, X.Y. Zhang (Abstract 2008). "Cosmetic Effect Of LPL Therapy On Wound & Burn Healing", 29th Annual Meeting of Japan Society for Laser Surgery & Medicine (JLSLM), 15-16 November 2008, Tokyo, Japan.
- ↪ F.A.H. Al-Watban (Abstract 2008). "The World Academy for Laser Applications (WALA): Its activities, Present & Future Plans", 29th Annual Meeting of Japan Society for Laser Surgery & Medicine (JLSLM), 15-16 November 2008, Tokyo, Japan.
- ↪ F.A.H. Al-Watban, B.L. Andres and X.Y. Zhang (Abstract 2008). "The Cosmetic Efficiency of Laser Therapy for Wound & Burn Healing", International congress in Aesthetic, anti-Aging Medicine & Medical Spa" 29 November - 01 December 2008, Dubai, UAE.

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

- Proctored 21 examinees for Medical Laser Safety Officer (MLSO), Aesthetic Laser Operator (ALO) and Surgical Laser Operator (SLO) Certifications.
- The Laser Medicine Research Section in conjunction with Elegant Training is organizing and actively promoting the “WALA Laser 2009 Universal Conference And Exhibitions With Anti-Aging & Aesthetic Symposium” to be held at the Bahrain International Exhibition Center, Manama, Kingdom of Bahrain on 18-21 October 2009 (www.walalaser-antiaging2009.com).

PEER-REVIEW

- ↔ “The Effect of Visible and Infra-Red Polarized Light (580-3400nm) on the Healing Process of Full-Thickness Skin Wounds: An experimental Study”, Iordanu, Panagiota,

et al., *Photomedicine and Laser Surgery*. Reviewed on January 2008.

- ↔ “Anti-apoptotic pathway of low level light irradiation in NO donor induced SH-SY5Y neuroblastoma cell lines”, Lim, Won Bong, et al., *Lasers in Surgery & Medicine*. Reviewed on July 2008.
- ↔ “Comparison of the Effects of the Pulsed Ultrasound and Low Level Energy Laser Irradiation on Macroscopic and Histopathological wound Healing: an Experimental Study”, Tikiz, Canan. *Lasers in Surgery & Medicine*. Reviewed on July 2008.

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.

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.

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

Head of Unit:

Ahmed A. S. Al-Qahtani, PhD

Members:

Mohammed N. Al-Ahdal, PhD

Alwaleed Alaidan, PhD

Abdulrahman Al-Suwaine, PhD

Suhair Abu-Zaid, MSc

Marie Fe Bohol, BS

Damian Dela Cruz, DVM

SPECIAL ACCOMPLISHMENTS

- Senior Editorship of the Journal of Infection in Developing Countries.
- Molecular typing of highly pathogenic avian influenza virus (H5N1).
- Studying host-genetics and its role on development of infection-related diseases. We have studied the role of genetic polymorphisms in Toll like receptors in relation to HBV and HCV infection.
- 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.
- Board membership of the Saudi Society of Clinical Laboratory Sciences.
- Collaborate with various Saudi Universities in supervision of graduate students.
- Consultations to the Medical Genetics Chair at King Saud University.
- Advisory activity with the Hajj and Umrah Center at Umm Al-Qura University.
- Training of students on molecular techniques in microbiology.
- Chairing the National Committee for Biosimilars Guidelines (SFDA).
- Membership of the National Committee for Poliomyelitis Eradication (MOH).
- Submission of two major research proposals to and the projects are as follows:
 - ∞ Molecular genetic analysis of Hepatitis C Virus (HCV) in relation to resistance to treatment.
Principal Investigator: Ahmed Al-Qahtani, PhD (MVID)
Co-Investigators: Mohammed Al-Ahdal, PhD (MVID), Ayman Abdo, MD (KKUH), Faisal Sanai, MD (Riyadh Military Hospital), Hanif Khalak, MSc (KFSHRC)
Proposed fund: 2,500,000 Saudi Riyals.
 - ∞ Clonal Distribution of Meticillin-Resistant Staphylococcus aureus in Saudi Arabia.

Principal Investigator: Alwaleed Al-Aidan, PhD (MVID)

Co-Investigators: Mohammed Al-Ahdal, PhD (MVID), Ahmed Al-Qahtani, PhD (MVID), Sahar Al-Thawadi, MD (Pathology, KFSHRC)
Proposed fund: 804,000 Saudi Riyals.

RESEARCH PROJECTS

Project Title: Effect of HBV and HCV Chronic Infection on the Amplification of C-myc and HER-2/neu Proto-Oncogenes and the Tumor Suppressor Gene, p53, in HCC in Saudi Patients, (RAC 2060024) .

Investigators: Tahani Al-Hazzani, Ahmed Al-Qahtani, PhD (MVID) , Abdul Monem Al-Ghamdi, MD (Pathology, KFSHRC), Hadeel Al-Manea, MD, (Pathology, KFSHRC) Mohammed Al-Ahdal, PhD (MVID)

PROJECT DESCRIPTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) constitute a serious public health problem worldwide. Hundreds of millions of people are infected in almost all parts of the world and infection with both viruses claim more than 2 million lives every year. Also, both viruses cause significant liver diseases in the Kingdom and they are hypothesized to be major causative agents for liver cirrhosis and hepatocellular carcinoma (HCC).

HCC development reflects a complex web of inter-related factors: host, viruses, and environment. As a result, the exact mechanisms that determine the disease outcome are yet to be clearly defined. This project was undertaken to study the chromosomal status of Her2/neu and c-myc oncogenes and the tumor suppressor gene p53 using Fluorescence in situ Hybridization (FISH) technique. Twenty slides from paraffin embedded HCC samples associated with either HCV or HBV were prepared for FISH analysis and hybridized with probes specific for each of the abovementioned genes. Each slide was also hybridized to centromeric probes specific for

the chromosomes that carry the gene under study. Two-hundred nuclei were counted to calculate the ratio of gene-to-centromere for each gene separately. Our preliminary results indicate that there is a significant amplification of Her2/neu and c-myc oncogenes in all samples studied. However, the status of p53 gene is either unchanged or slightly underrepresented indicating some gene deletion. All results are still pending statistical analysis to draw meaningful conclusions.

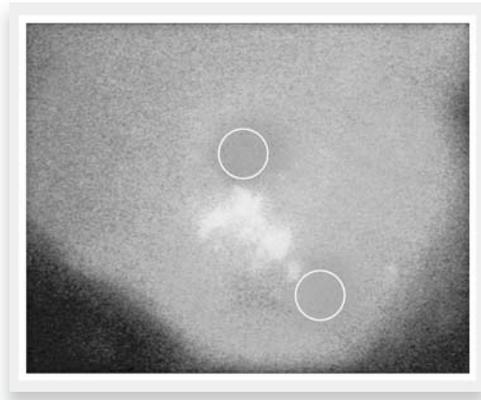


Figure 1: Her-2/neu amplification (red) in tissue sample taken from HCC sample associated with HBV infection. Centromeres are evident (encircled areas).

Project Title: Host genetic Polymorphism in Toll-Like Receptors and Disease Outcome in Hepatitis B and C virus-infected Saudi Patients, RAC 2060040.

Investigators: Ahmed Al-Qahtani, PhD (MVID), Hamad Al-Ashgar, MD (KFSHRC), Khalid Al-Kahtani MD (KFSHRC), Ayman Abdo, MD, (KKUH), Faisal Sanai, MD, Riyadh Military Hospital, Mohammed Al-Ahdal, PhD (MVID),

PROJECT DESCRIPTION

Toll like receptors (TLRs) are a group of proteins that are responsible for initiating innate host defense system. A wide range of pathogens, from virus to bacteria, is detected by host using this system of receptors. To date, 10 TLRs have been described in

the human genome. Activation of TLRs leads to the induction of immune-related genes that are extremely essential for an effective immune response required to control infection. In this study, we studied single nucleotide polymorphisms (SNPs) in TLR2 and TLR4 in patients infected with either HBV or HCV. Using blood samples from one-hundred Saudi patients for each virus, the carboxy terminus of TLR2 was amplified and sequenced to study 10 SNPs located at this region. Amplification and sequencing were successful and our preliminary results showed significant association with chronic infection and two SNPs, namely Pro631His and Arg753Gln. Additionally, two SNPs (Asp299Gly and Thr399Ile) that are known to cosegregate together are studied in TLR4 using TaqMan DNA technology. Our preliminary results indicate positive association with chronic infection with both viruses. We plan to analyze more samples and use appropriate statistical programs to reach comprehensive conclusions on the role of these variants on viral infections in the Saudi populations.

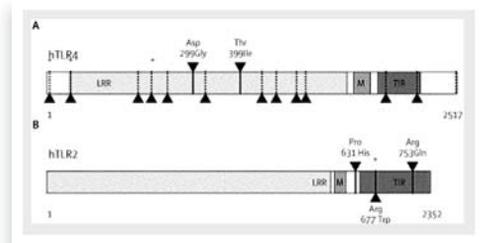


Figure 2: SNPs in TLR2 and TLR4 that are investigated in this study.

Project Title: Clonal Distribution of Meticillin-Resistant *Staphylococcus Aureus* in Saudi Arabia, RAC # 2080054

Investigators: Alwaleed Alaidan, PhD, Marie F. Bohol, BS, Ahmed Al-Qahtani, PhD, Sahar Al-Thawadi, MD, Mohamed Al-Ahdal, PhD

PROJECT DESCRIPTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) were first reported in 1961 and have since

become a major nosocomial pathogen worldwide. Major concern is the emergence of vancomycin-intermediate *S. aureus* (VISA) and more recently vancomycin-resistant *S. aureus* (VRSA). The reservoir of MRSA is infected and colonized patients, and the major mode of transmission from patient to patient is on the contaminated hands of healthcare workers. It is axiomatic that the sooner an MRSA infection is diagnosed, and the susceptibility to antimicrobial agents established, the sooner appropriate therapy and control measures can be initiated. Laboratory diagnosis and genotyping are crucial steps in treating, controlling and preventing MRSA infections. Few studies have been done to report the prevalence of MRSA in Saudi Arabia, and they have indicated that a diverse number of circulating MRSA strains have been detected in several major hospitals. This study performed to track the presence of MRSA strains in five province in Saudi Arabia, to give an idea about the actual spread of MRSA nationwide and to perform comparative chromosomal DNA analysis of MRSA strains for epidemiological investigation using pulsed-field gel electrophoresis, which will help further studies for the ideal ways to combat and control the spread of such a serious organism.

Project Title: Molecular typing of Multiresistant Isolates of *Acinetobacter baumannii*, RAC #2060031

Investigators: Buthainah Al-Shahrani Alwaleed Alaidan, PhD, Marie F. Bohol, BS, Ahmed Al-Qahtani, PhD, Mohamed Al-Ahdal, PhD

PROJECT DESCRIPTION

A. baumannii is an important opportunistic pathogen that is rapidly evolving toward multidrug resistance and is involved in various nosocomial infections that are often severe. It strongly prompts the epidemiological study of *A. baumannii* infections. However, there is no a generally accepted typing scheme. Different genotypic and phenotypic procedures were evaluated for the characterization of clinical isolates of *A. baumannii*. Aims of this study are to find the most suitable methods to discriminate *A. baumannii*

clinical isolates. Investigate the clonal distribution of *A. baumannii*, obtain data on the diversity of clinical isolates of *A. baumannii*, and determine whether the increasing appearance of resistant *A. baumannii* is due to the spread of an epidemic strains or not. In the present study we collected *A. baumannii* isolates from patients hospitalized in KFSH&RC and genotype these isolates by several techniques {Pulsed-Field Gel Electrophoresis (PFGE), Amplified rDNA Restriction Analysis (ARDRA), Random Amplified Polymorphic DNA analysis (RAPD)} and evaluate their applicability for the identification of *A. baumannii* at the strain level. Our results, evaluate different genomic fingerprinting methods performed by computerized comparison of digitized fingerprinting patterns (in RAPD & PFGE analysis) is easier and gives an accurate analysis compared to visual comparison (ARDRA analysis) for large numbers of samples tested. Data analysis offers the possibility of comparison of large numbers of patterns, formation of databases, and cluster analysis. Moreover PFGE technique was shown to be most suitable method for differentiating strains from hospital outbreaks. For the reason that PFGE fingerprints are highly reproducible, interpretation is fairly straightforward.

Project Title: Detection and Genotyping of Human Papillomavirus in Cervical Samples from Saudi Patients, RAC # 2060038.

Investigators: A. Al-Suwaine. A. Al-Qahtani, A. Munkarah, A. Tulbah, L. Asaad, A Alaidan, M. Fe Bohol, and M. Al-Ahdal

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 rang 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 (Figure 1). The HPV positive samples

were subsequently genotyped by reverse hybridization blot assay to identify the high risk genotypes in Saudi Arabia.

PROGRESS

Completed.

The project has identified more than 100 paraffin embedded cervical samples. The most prevalent HPV genotypes were HPV 16 (60%) followed by HPV 18(10%), and others were found to be HPV 45, 33, 31, 52, 53, 58, 59 and 66.

PUBLICATIONS

- ↪ Al-Mozaini M, Bodelon G, Karstegl CE, Jin B, Al-Ahdal M, Farrell PJ. Epstein-Barr virus BART gene expression. *J Gen Virol.* 2009 Feb;90(Pt 2):307-16.
- ↪ Tayeb HT, Dela Cruz DM, Al-Qahtani A, Al-Ahdal MN, Carter MJ. Enteric viruses in pediatric diarrhea in Saudi Arabia. *J Med Virol.* 2008 Nov;80(11):1919-29.
- ↪ Al-Qahtani A, Siddiqui YM, Bakheit AA, El-Sayed OA, Aboul-Enein HY and Al-Ahdal MN. Inhibition of growth of *Leishmania donovani* promastigotes by newly synthesized 1, 3, 4, Thiadiazole Analogs. Submitted.
- ↪ Alzahrani AJ, Dela Cruz DM, Obeid OE, Bukhari HA, Al-Qahtani AA and Al-Ahdal MN. .Molecular detection of Hepatitis B, Hepatitis C and Torque Teno viruses in drug users in Saudi Arabia. *J Med Virol.* In press.
- ↪ Khan MA, van der Wal M, Farrell DJ, Cossins L, van Belkum A, Alaidan A and Hays JP. Analysis of VanA vancomycin-resistant *Enterococcus faecium* isolates from Saudi Arabian hospitals reveals the presence of clonal cluster 17 and two new Tn1546 lineage types. *Journal of Antimicrobial Chemotherapy.* 2008 Aug; 62(2): 279-83.
- ↪ Ghanem A, Aboul-Enein HY, El-Azzouny A, El-Beairy MF, Al-Humaidi E, Alaidan AA, Amin K, Al-Ahdal M N. Direct enantioselective HPLC monitoring of lipase-catalyzed kinetic resolution of tiaprofenic acid in nonstandard HPLC organic solvents. *Chirality.* 2008 Aug;20(8):871-7

POSTER

- ↪ A. Al-Suwaine, L. Assad, A. Tulbah, A. Alaidan, M. Bohol, J. Al-Subhi, I. Al Badawi, H. Salem, A. Munkarah PREVALENCE OF HPV DNA IN CERVICAL CANCER IN SAUDI PATIENTS . 12 th Biennial Meeting of the International Gynecologic Cancer Society, Bangkok, Thailand, October 25-28, 2008.
- ↪ Alwaleed Alaidan; Bohol, Marie Fe; Buthainah Al-Shahrani 2009 Molecular typing of Multiresistant isolates of *Acinetobacter baumannii* .KFSH&RC Annual Research Report King Faisal Specialist Hospital & Research Centre.

THE DEPARTMENT OF
BIOMEDICAL PHYSICS



The Department of Biomedical Physics

The Department has continued to launch initiatives to fulfill the goals and objectives set for its four major areas of responsibilities, namely (1) service, (2) consultation, (3) research, and (4) continuing education. High priority has been placed on the provision of state-of-the-art services to the clinical care departments at KFSH&RC, mainly in support of radiation therapy patient treatment as well as establishment and management of programs for medical radiological imaging and radiation protection in conformance with recognized international standards. This is in addition to the conduct of clinical and applied research, delivery of professional continuing education programs, and pursuing of income generating activities through scientific research grants and professional service contracts. Although resignations and recruitment difficulties caused a period of instability over the past year, there were substantial achievements and growth of services among which are the following:

- Optimization of clinical medical physics services for cancer patients undergoing radiotherapy treatment.
- Five (5) fold increase of patients being planned using IMRT (Intensity Modulated Radiation Therapy) covering 37 treatment sites.
- Budget approval for the purchase of four major state-of-the-art radiotherapy equipment (CyberKnife, Tomotherapy, RapidArc and Large Bore CT) for cancer patient treatment.
- Hosting of the International Atomic Energy Agency (IAEA) regional training workshop, the 3rd International Saudi Medical Physics Conference, and the Nuclear Medicine training course and workshop.
- Publication of research papers and approval of a number of KACST grant projects for the Department.

Chairman:

Belal Mofteh, PhD, MCCPM

Deputy Chairman:

Ghazi Alsbeih, MD, PhD

Administrative Support Staff:

Irene Banguilan, BSc

Anna Nabong, BSc (until June 2008)

Mildred San Pedro, BSc

Josephine Veridiano, BSc

- Collaboration with national and international institutions as well as regulatory agencies on service, research and education levels.
- Increase in the calibration and TLD radiation monitoring services output.
- Development of staff expertise through the department continuing education program: (1) Board certification of our health physicist (Mr. Ibrahim Al-Anazi, Saudi) by the American Board of Health Physics; (2) Board certification of two medical dosimetrists (Mr. Salter Lee, Australian and Mrs. Wedyan Safar, Saudi) by the American Board of Medical Dosimetry. Mrs Safar is the first Saudi trained locally at KFSH&RC to pass the American Medical Dosimetry board exam; (3) KACST Radiation Safety Officer licensure in Nuclear Medicine of our Health Physics staff (Mr. Ibrahim Al-Gain, Saudi).

Highlights of activities in 2008 for the following sections and core facilities are shown in separate reports:

SECTIONS

- Radiation Physics
- Imaging Physics
- Health Physics
- Biomedical Physics Research

CORE FACILITIES

- Radiation Safety Office
- Gamma Irradiation Facility
- Clinical Dosimetry and Treatment Planning Unit

The Department will continue to explore further initiative to facilitate interdisciplinary programs that address the Department's current and future challenges in order to contribute significantly to the KFSH&RC's core mission of providing high quality patient care.

RESEARCH PROJECTS

Staff members of the Department are engaged in various research activities and involved in a broad range of research collaboration. The external funding available to the department continues to grow. A number of research projects are in progress and were completed during this reporting period. Status of research projects is detailed in the sectional reports.

FUTURE RESEARCH DIRECTION

The Physics Department will continue focus its research programs in carefully selected strategic directions. Future research will be conducted with primary focus on improving quality of patient care. The future research direction of the Department is defined in the respective reports of the Department's sections and core facilities.

PUBLICATIONS

Our publication activity remains high. The Department has published a number of papers, from approved research projects, in international journals. Details of 2008 publications are listed in each section/core facility report.

Biomedical Physics Research

The Radiation Biology section 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 tissues' complications probability (NTCP) using predictive assays for radiosensitivity. 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.

Head of Unit:

Ghazi Alsheih, PhD

Members:

Najla Al-Harbi, BSc

Muneera Al-Buhairi, BSc

Khaled Al-Hadyan, BSc

Sarah Al-Qahtani, BSc

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 (PhD), N. Al-Rajhi (MD), A. Alaam (MD), M. Al-Sebaie (MD), Najla Al-Harbi (BS) and Muneera Al-Buhairi (BS)

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

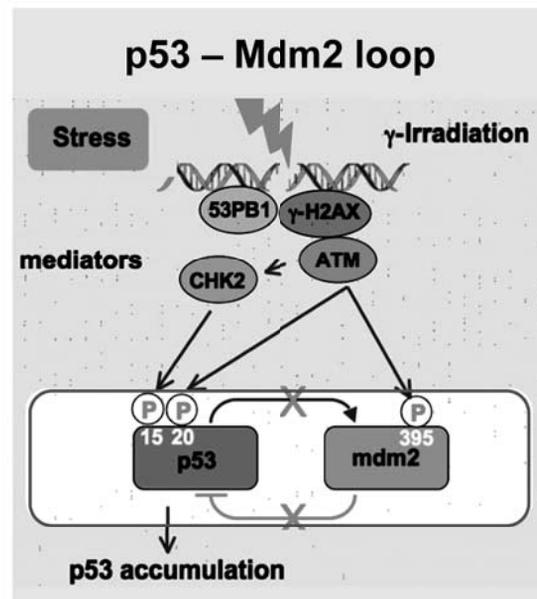
In this progress report we studied the Involvement of MDM2 Promoter T309G and TP53 G72C Polymorphisms in Radiation Sensitivity and Cancer Predisposition.

PURPOSE/OBJECTIVE

Genetic variations are frequent in humans and single nucleotide polymorphism (SNP) in genes involved

in pathways related to cell-cycle control, DNA repair and apoptosis are likely to affect radiation sensitivity and cancer susceptibility. The two major proteins along this pathway are p53 and its negative regulator MDM2. MDM2 is an ubiquitin ligase that plays a critical role in regulating levels and activity of p53 protein, which is a central tumor suppressor. Functional polymorphisms in both MDM2 and TP53 genes have been identified. A SNP in the intronic promoter of the human MDM2 gene (SNP309

T/G) occurs at frequencies dependent on demographic history. This SNP309 has differential effects on MDM2 and p53 proteins' activity and associates with altered risk for the development of several cancers. The SNP TP53 codon 72 G/C (Arg/Pro) is more common in the general



population. Molecular studies showed that the variant 72C allele can alter the transcription of p53 target genes and modify the apoptotic potential of cells. This SNP was suggested to associate with the onset and risk of different cancers.

MATERIALS/METHODS

We investigated the association between these two SNPs and the risk to develop Head and Neck cancer in a cohort of 421 individuals (138 cancer patients and 283 controls) of Middle-Eastern origin. In addition, association with cellular radiosensitivity studied by clonogenic survival was investigated in 105 skin fibroblast cell strains established from volunteers and cancer patient.

RESULTS

Data showed a highly significant association between MDM2 309 T/G ($P < 0.001$) but not TP53 72 G/C ($P = 0.40$) and cancer occurrence. However, both polymorphisms were significantly associated with cellular sensitivity to ionizing radiation ($P = 0.03$ and $P = 0.05$ for MDM2 309 T/G and TP53 72 G/C, respectively).

Sequencing Results: Patients with Cancer						
Gene SNP	Cancer = 45y/o	Cancer > 45y/o	OR (CI)	P =	Mean Age (Range / years)	P =
p53: (#)	(80)	(82)				
G/G:	24	25			45.8 (19-77)	
G/C:	41	32	1.33 (0.61-2.94)	0.43	44.6 (15-72)	0.40
C/G:	15	25	0.63 (0.24-1.59)	0.27	47.5 (17-69)	
G	89	82				
C	71	82	0.80 (0.50-1.26)	0.31		
Mdm2: (#)						
T/T:	35	36			45.3 (15-72)	
T/G:	33	31	1.09 (0.53-2.28)	0.79	46.2 (18-77)	0.94
G/G:	12	14	0.88 (0.33-2.38)	0.78	45.5 (17-71)	
T	103	103				
G	57	59	0.97 (0.60-1.56)	0.88		

Sequencing Results: Cancer Patients vs. Control				
Gene SNP	Cancer Patients	Control Individuals	OR (CI)	P =
p53: (#)	(163)	(265)		
G/G:	49	83		
G/C:	74	109	1.15 (0.71-1.87)	0.55
C/G:	40	73	0.53 (0.53-1.62)	0.77
G	172	275		
C	154	255	0.97 (0.73-1.62)	0.80
Mdm2: (#)				
T/T:	71	74		
T/G:	65	139	0.49 (0.31-0.77)	0.001
G/G:	26	77	0.35 (0.20-0.63)	0.0002
T	207	287		
G	117	293	0.55 (0.41-0.74)	0.00003

Sequencing Results: Radiation Sensitivity				
Gene SNP	Sensitive SF2 < 0.35	Control SF2 = 0.35	OR (CI)	P =
p53: (#)	(52)	(63)		
G/G:	22	16		
G/C:	21	27	0.57 (0.22-1.46)	0.19
C/G:	9	20	0.33 (0.10-1.01)	0.03
G	65	59		
C	39	67	0.53 (0.30-0.93)	0.02
Mdm2: (#)				
T/T:	21	19		
T/G:	25	28	0.81 (0.33-1.99)	0.61
G/G:	5	16	0.28 (0.07-1.05)	0.03
T	67	66		
G	35	60	0.57 (0.07-1.02)	0.04

CONCLUSION

Our data suggest that MDM2 promoter 309 T/G polymorphism predisposes to cancer of Head and Neck in our population and also influence radiosensitivity. These findings may have important implications for both cancer risk and individualizing cancer treatment with radiotherapy. Supported by KFSH&RC grants 2000 031 and 2040 025.

FUTURE RESEARCH DIRECTION

While finalizing experiments and data analysis of this project, we start working on new project related to cervix carcinoma: HPV infection, genetic predisposition and biomarkers of response to chemo-radiation therapy.

PUBLICATIONS

MANUSCRIPTS

- ↪ G. Alsbeih, K. Al-Hadyan, N. Al-Harbi. Assessment of carriers' frequency of a novel MRE11 mutation responsible for the rare ataxia telangiectasia-like disorder. *Genetic Testing*. Jul 24, 12(3), 1-4, 2008.
The abstract was also indexed under Specific disorders in Specific Communities in the Community Genetics Network Newsletter, Number 14, October 2008.
- ↪ Christophe Badie, Sylwia Dziwura, Claudine Raffy, Theodora Tsigani, Ghazi Alsbeih, John Moody, Paul Finnon, Ed Levine, David Scott, Simon Bouffler. CDKN1A gene expression after irradiation as a marker of skin responses to radiotherapy. *British Journal of Cancer*. Jun 3; 98(11), 1845-51, 2008.

ABSTRACTS/CONGRESS PROCEEDINGS

- ↪ Ghazi Alsbeih, Medhat El-Sebaie, Najla Al-Harbi, Muneera Al-Buhairi, Khaled Al-Hadyan, Nasser Al-Rajhi. Involvement of MDM2 Promoter T309G and TP53 G72C Polymorphisms in Radiation Sensitivity and Cancer Predisposition. Annual Meeting of the European Society for Therapeutic Radiology and Oncology (ESTRO), Goteborg, Sweden, 14-18 September, 2008.
- ↪ Zeenath Jehan, Prashanth Bavi, Azhar Hussain, Ghazi Alsbeih, Nasar Al-Sanea, Alaa Abdul Jabbar, Luai Asharu, Samar Alhomoud, Fouad Al-Dayel, Shahab Uddin, Khawla Al-Kuraya. PIK3CA amplification is an independent predictor of better survival in colon cancer patients of Middle East. AACR, San Diego, CA. 12-16 April, 2008.
- ↪ Mashaal Al-Khaldi, Muneera Al-Buhairi, Najla Al-Harbi, Khaled Al-Hadyan, Jamal Sharaf, and Ghazi Alsbeih. Application of radiobiological models in the prediction of normal tissues complications to radiotherapy. 3rd International Saudi Conference on Medical Physics, KFSHRC, 5-7 Feb. 2008.
- ↪ Khaled Al-Hadyan, Najla Al-Harbi, Mohamed Rajab, Muneera Al-Buhairi, Ghazi Alsbeih. Frequency of Mre11 G630C mutation responsible for the rare ataxia telangiectasia-like disorder in Saudi Arabia. 1st KFSH&RC Resident's Research Day, 30 January 2008.

Clinical Dosimetry and Treatment Planning Unit

In 2008 there was a five (5) fold increase of patients being planned using IMRT (Intensity Modulated Radiation Therapy) covering 37 treatment sites over 2007. IMRT provides better dose coverage for tumors and minimization of dose to critical organs and normal tissue.

CT planning for breast was introduced and for 2008, every breast patient was CT planned using field in field method for missing tissue compensation to provide more homogenous dose distribution.

Next year, 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. Rapid Arc, Tomotherapy and Cyberknife treatment machines are being installed and each of these machines provide further treatment options and further improved coverage of the tumors while sparing the normal tissue and critical organs.

Head of Unit:

Michael Lim, CMD, ACT

Members:

Ghadeer Nazer, BSc

Hind Al-Selham, BSc

Huda Al-Mohammed, BSc, CMD

Lee Salter, BSc, CMD

Paula Yates, RTT, CMD

Wedyan Safer, BSc, CMD

Ericka Venturina, BSc

CORE SERVICE ACTIVITIES

ACTIVITIES	YEAR 2008
MU Calculation	570
TBI Calculation	58
3D CT Treatment Planning	1070
2D Contour Treatment Planning	100
Stereotactic Radiosurgery/Radiotherapy	18
Electron Cutout Measurement	107
TLD Dosimetry	58
HDR Brachytherapy	15
LDR Brachytherapy	14
IMRT	143
Clinical Consultation	48
TOTAL PROCEDURES	2201
PATIENTS	1372
MANHOURS	8322

TRAINING AND EDUCATION ACTIVITIES

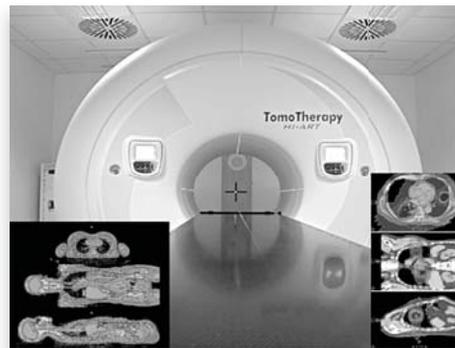
Mr.Lee Salter and Ms.Wedyan Safer passed their Medical Dosimetrist Certification Board examination and are now Board Certified Dosimetrists. Congratulations to both. Ms.Wedyan Safer is the first locally trained Dosimetrist in Saudi Arabia to obtain the Board Certification.

We continue to provide training in clinical dosimetry and treatment planning to physics graduates from different universities within the kingdom.

NEW TREATMENT MACHINES APPROVED FOR ACQUISITION IN 2008



CYBERKNIFE



TOMOTHERAPY



RAPID ARC

Gamma Irradiation Facility

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

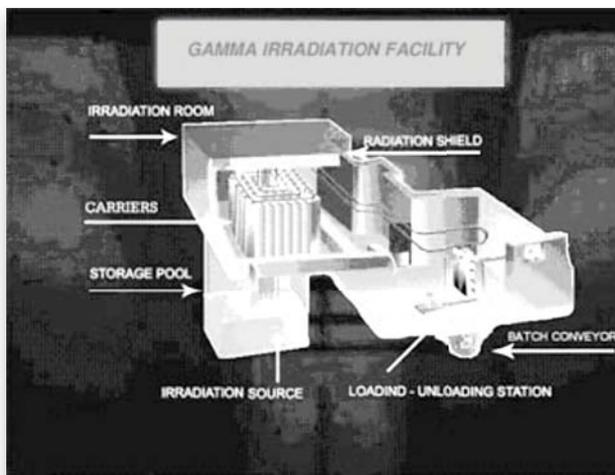
Head of Unit:

Akram Al-Moussa, BSc

Members:

Saad Bin-Jamaan, BSc

Edilberto Delos Reyes



CORE SERVICE ACTIVITIES

The activities of the Gamma Irradiation Facility in 2008 are as follows:

1. Continued to provide sterilization for hospital needs (Cyclotron kits and supplies of ART laboratory.
2. Provided gamma irradiation services for Two Master Degree student from King Saud University, College of pharmaceutical science, and the other from Riyadh College for Medical, Dental and Pharmaceutical sciences, with doing the necessary dosimetry for these samples.)
3. Renewal of ISO certification, auditing was done successfully without any major or minor comment.
4. Research project with KACST on the film dosimetry are going very well, trying to modify a new high dose dosimeter.

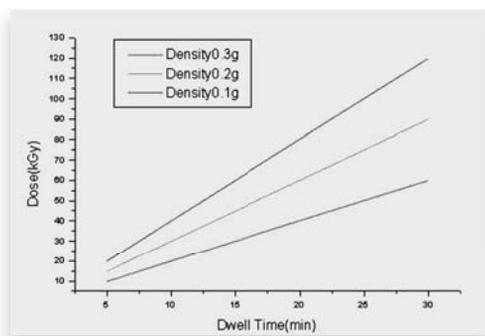


Figure 1. Relationship between Dwell Time and Dose for Materials of Different Densities.

5. New proposed strategy for running GIF was investigated taken in consideration applications that can only be sterilized in GIF.

GAMMA RAY STERILIZATION

The Gamma Irradiation Facility has continued to provide sterilization services for the Hospital departments and other institutions on a fee for service basis. Sterilization of different items such as pharmaceuticals for Tabuk Company, Gallope Co. and Riyadh Pharma and some frequent customers, such as National Guard Hospital. About 115,711 SR was the income of GIF last year. The Facility will pursue its income generating opportunities through sterilization of medical products/materials using gamma irradiation.

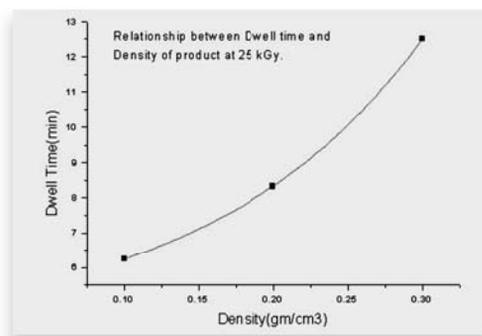


Figure 2. Relationship between Dwell Time (time of irradiation) and Density of Irradiated Materials.

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. 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.

Head of Unit:

M. Gary Sayed, PhD

Members:

Abdallah Al-Haj, PhD

Amal Al-Mutairi,

Celestino S. Lagarde, BSc

Heba Al-Humaidan, BSc

Ibrahim Al-Gain, BSc

Nabil I'Qilan, MSc

Rana Al-Qwiz

Rami Al-Harbi

RESEARCH ACTIVITIES

The table below summarizes the accomplishments made by the Health Physics Section for year 2008 in providing services to the KFSH&RC institution, to other facilities in the Kingdom of Saudi Arabia and surrounding countries in the Gulf region (Figure 1).

Task	Quantity
Radiation workers monitored for occupational doses	24876
Patients surveyed for radiation level	324
Patients rooms surveyed for radiation level	324
Patients rooms decontaminated	312
Equipment surveyed for contamination	37
TLD badges irradiated for quality control of TLD readers of outside facilities	44
Consultative advice provided	4
Training courses & educational lectures provided	12 + Others

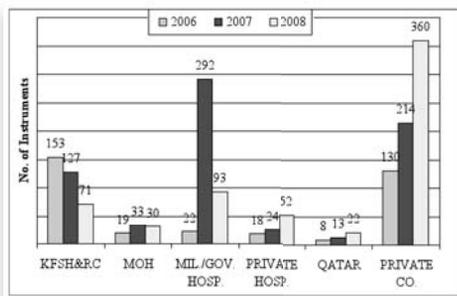


Figure 1. Graph showing the number of instruments and institutions that are being served for instrument calibration in year 2008.

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.

FUTURE RESEARCH DIRECTION

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

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.

Head of Unit:

Kostas Chantziantoniou, MSc, DABR

Members:

Refaat Y. Al-Mazrou, MSc, MIPEM

Adnan Z. Al-Watban, PhD

Omer Demirkaya, PhD

Nabil I'Qilan, MSc

RESEARCH PROJECTS

Project Title: Lesion Quantification in Whole Body Images of Positron Emission Tomography (PET)

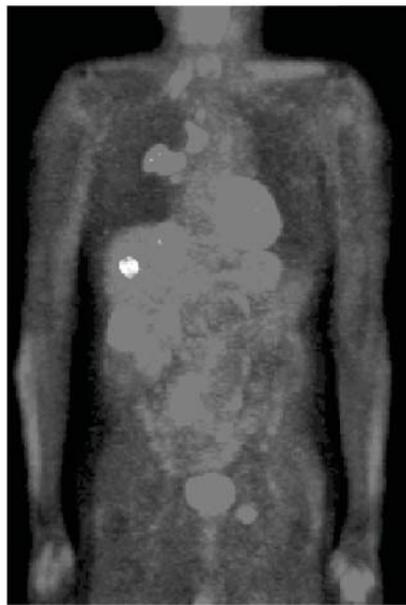
Investigator: O. Demirkaya

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 SUV values from a lesion volume. It may also allow them to track small changes in lesion characteristics, which may be difficult to observe visually.

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.



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.

PUBLICATIONS

ABSTRACTS ACCEPTED FOR PRESENTATION

- ↪ Omer Demirkaya, "Diffusion Filtering of Functional Images Using the Structural Information Available in Hybrid Imaging Modalities" IEEE 2008 Nuclear Science Symposium, Dresden, Germany.

MANUSCRIPTS APPROVED FOR PUBLICATION

- ↪ L. Al-Haj, W. Al-Ahmadi, M. Al-Saif, O. Demirkaya, and K. Khabar, "Cloning-free regulated monitoring of reporter and gene expression," *BMC Molecular Biology*, vol. 10, p. 20, 2009.

BOOKS

- ↪ Image Processing with MATLAB: Applications in Medicine and Biology, Omer Demirkaya,

Musa H. Asyali, Prasanna Sahoo, *CRC Press: Taylor & Francis Group, Boca Raton, USA, 2008.*

Radiation Physics

The Radiation Physics Section provides clinical radiation oncology physics and quality assurance services to cancer patients undergoing radiotherapy treatment. 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; development and introduction of new treatment techniques for clinical services; providing consulting services to other radiation oncology centers in the Kingdom; training graduate students from institutions of higher education and radiation therapy physicists from other cancer centers. The Clinical Dosimetry and Treatment Planning Unit of this section performs all treatment planning and clinical dosimetry services for radiation therapy patients.

In 2008, the number of Intensity Modulated Radiation Therapy (IMRT) patients increased significantly. We have treated more than 140 IMRT patients, covering more than 37 tumor sites. IMRT is an advanced mode of high-precision radiotherapy treatment which introduction into clinical practice is a major accomplishment for this institution.

Three state-of-the-art radiotherapy machines have been approved for purchase to provide our KFSH&RC cancer patients with the best-diversified treatment options. With the acquisition of these new modalities, 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 in one single institution.

We will also pursue the development and implementation of other innovative radiotherapy techniques such as IGRT and IORT as well as engineering of affiliation contracts with major radiotherapy vendors to turn KFSH&RC into a reference site for Saudi Arabia and Middle East customers. This is in line with our mission of turn our services a centre of excellence in clinical medical physics and radiation oncology.

Head of Unit:

Belal Mofteh, PhD, MCCPM

Members:

Mohd Abdullah Al-Kafi, MSc

Huda Al-Mohammed, MSc

Waleed Al-Najjar, PhD, ABR, ABMP

Raju Francis Alookkaran, MSc

Hind AlSelham, BSc

Eman Al-Sulaimani, MSc

Sarah Ashmeg, BSc

Manal Awidh, BSc

Omar Chibani, PhD

Tarek El-Kaissi, PhD

Zeinab Hassan, PhD

Michael (Lam Faat) Lim, CMD

Fareed Mahyoub, MSc

Ghadeer Nazer, BSc

Ahmed Nobah, MSc

Wedyan Safer, BSc, CMD

Lee Salter, BSc, CMD

Paula Michelle Yates, CMD

RESEARCH PROJECTS

Project Title: Establishment of a Monte Carlo-based Clinical Dosimetry Center in Saudi Arabia, Project # 2060 026.

Principal Investigator: Belal Mofтах

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, a computer cluster was acquired for the Monte Carlo project. Few more clinical parameters have been calculated and compared with measurements. Two abstracts are being prepared to be submitted to the World Congress of Biomedical Physics, to be held in September 2009, Germany. (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. Four new innovative IGRT systems (RapidArc, TomoTherapy, CyberKnife, 4D Big-Bore

CT) have been acquired 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 IGRT cutting-edge techniques in one single institution. A research proposal will be drafted and submitted.

Project Title: Incorporation of new imaging modalities (PET/CT and MRI Sim) into Radiation Treatment Planning.

PROJECT DESCRIPTION

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

PROGRESS

Research in preparation. Multi-disciplinary research group from different KFSH&RC departments will be formed. PET/CT software was acquired while a tender for an MRI Sim was submitted. A research project will be submitted.

PUBLICATIONS

PUBLICATIONS IN PEER-REVIEWED JOURNALS

- ↪ Kay-Uwe Kasch, Belal A. Mofтах, Evaluation of the potential in radiation dose reduction for full-field digital mammography, *Pol J Med Phys Eng.* 2008;14(2):87-98.

CONFERENCE PROCEEDINGS AND ABSTRACTS

- ↪ Belal Mofтах, A. Nobah, T. El-Kaissi, W. Al-Najjar, IMRT *In-Vivo* Dose Verification Using 2D-Array Detector

and Electronic Portal Imaging Device (EPID), Abstract Booklet of the 16th International Conference on Medical Physics (ICMP 2008), Dubai, April 14-16, 2008.

- ↔ Belal Mofteh, M Abdullah Al Kafi, Clinical Application and Validation of Monte-Carlo Simulation Codes EGSnrc and BEAMnrc for Radiotherapy Photon Beams, Abstract Booklet of the 16th International Conference on Medical Physics (ICMP 2008), Dubai, April 14-16, 2008.
- ↔ A. Nobah, S. Ashmeg, B. Mofteh, IMRT *in-vivo* dose verification using a commercially available transparent multi-wire ionization chamber, Abstract Booklet of the 16th International Conference on Medical Physics (ICMP 2008), Dubai, April 14-16, 2008.
- ↔ M Abdullah Al Kafi, Wamied Abdelrahman and Belal Mofteh, Calculation and Validation of Enhanced Dynamic Wedge Factors for Medical Linear Accelerators Using Eclipse Treatment Planning System, Abstract Booklet of the 16th International Conference on Medical Physics (ICMP 2008), Dubai, April 14-16, 2008.

PRESENTATIONS AT SCIENTIFIC MEETINGS: (PRESENTING AUTHOR DENOTED BY*)

- ↔ Belal Mofteh*, Commissioning: System Set-up and Machine Source Configuration (Patient Data Acquisition and Simulation), International Atomic Energy Agency (IAEA) Regional Training Course on Quality Assurance in Radiotherapy Treatment Planning Systems, KFSH&RC, Riyadh, Saudi Arabia, 19 April 2008 (Invited speaker).
- ↔ Belal Mofteh* and Michael Lim, Advanced Special Application in RTPS: Inverse Planning and Optimization, International Atomic Energy Agency (IAEA) Regional Training Course on Quality Assurance in Radiotherapy Treatment Planning Systems, KFSH&RC, Riyadh, Saudi Arabia, 20 April 2008 (Invited speaker).
- ↔ S. Vatrinsky*, E. Gershkevitch*, J. Van Dyk*, E. Gershkevitch*, S. Devic*, Belal Mofteh*, W. Al-Najjar*, M. Lim*, Measurements and Calculations, International Atomic Energy Agency (IAEA) Regional Training Course on Quality Assurance in Radiotherapy Treatment Planning Systems, KFSH&RC, Riyadh, Saudi Arabia, 21 April 2008 (Invited speaker).
- ↔ E. Gershkevitch*, S. Devic*, Belal Mofteh*, W. Al-Najjar*, M. Lim*, Calculations in Groups, International Atomic Energy Agency (IAEA) Regional Training Course on Quality Assurance in Radiotherapy Treatment Planning Systems, KFSH&RC, Riyadh, Saudi Arabia, 22-23 April 2008 (Invited speaker).
- ↔ Belal Mofteh*, A. Nobah, T. El-Kaissi, W. Al-Najjar, IMRT *In-Vivo* Dose Verification Using 2D-Array Detector and Electronic Portal Imaging Device (EPID), 16th International Conference on Medical Physics (ICMP 2008), Dubai, April 14-16, 2008.
- ↔ Belal Mofteh, M Abdullah Al Kafi*, Clinical Application and Validation of Monte-Carlo Simulation Codes EGSnrc and BEAMnrc for Radiotherapy Photon Beams, 16th International Conference on Medical Physics (ICMP 2008), Dubai, April 14-16, 2008.
- ↔ A. Nobah*, S. Ashmeg, B. Mofteh, IMRT *in-vivo* dose verification using a commercially available transparent multi-wire ionization chamber, 16th International Conference on Medical Physics (ICMP 2008), Dubai, April 14-16, 2008.
- ↔ M Abdullah Al Kafi*, Wamied Abdelrahman and Belal Mofteh, Calculation and Validation of Enhanced Dynamic Wedge Factors for Medical Linear Accelerators Using Eclipse Treatment Planning System, 16th International Conference on Medical Physics (ICMP 2008), Dubai, April 14-16, 2008.
- ↔ B. Mofteh*, Slobodan Devic, Té Vuong, Image Guided High Dose Rate Brachytherapy Using Multichannel Endorectal Applicators, 3rd International Saudi Symposium on Medical Physics, Riyadh, Feb 5-7, 2008.
- ↔ A. Nobah*, B. Mofteh, T. El-Kaissi, W. Al-Najjar, Clinical IMRT Dose Verification Using 2D-detector matrix and Electronic Portal Imaging Device (EPID), 3rd International Saudi Symposium on Medical Physics, Riyadh, Feb 5-7, 2008.
- ↔ M Abdullah Al Kafi*, Wamied Abdelrahman and Belal Mofteh, Calculation and Validation of Enhanced Dynamic Wedge Factors for Symmetric and Asymmetric Photon Fields Using Eclipse Treatment Planning System, 3rd International Saudi Symposium on Medical Physics, Riyadh, Feb 5-7, 2008.

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 IAEA.

Head of Unit:

Fareed H. Mayhoub, MSc

Members:

Ibrahim K. Al-Anazi, MSc, CHP

Celestino Lagarde, BS (Shared)

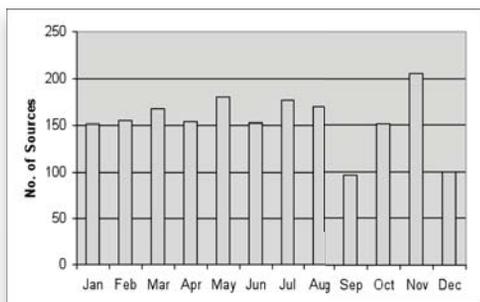


Figure 1. Graph showing the monthly out-going packages for year 2008.

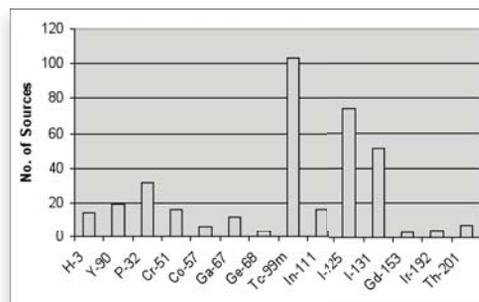


Figure 2. Graph showing the number of imported sources of radioactive isotopes in year 2008.

RSO ACTIVITIES

For the year 2008, the RSO applied for amendment and renewal of the KFSH&RC license from KACST for the radiation practices of Nuclear Medicine, and TLD Dosimetry 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 Scientific Research and the Secondary Standard Dosimetry Laboratory. One application for authorization to use radioactive materials was evaluated and obtained the RSC approval. In radiation measurements, there were 362 incoming sources and 1845 out-going packages of radioactive materials surveyed. In the principle of "As Low as Reasonably Achievable" (ALARA), 75 investigations were carried out on staff whose occupational doses exceeded the ALARA levels; 20 thyroid bioassays were performed. Four work areas and 2 equipments were surveyed for radiation and contamination levels. Seven work area were surveyed for shielding evaluation and verification. A total of 17 radioactive sealed sources were checked for inventory and 7 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 95

drums were surveyed and stored in Radioactive Waste Storage and 90 drums of wastes were disposed. In education and training the RSO conducted 3 in-house two-week course lectures to 30 members of Ministry of Defense. The RSO has maintained its linkage within the Hospital and with national and international bodies. Three RSC meetings were coordinated and the Office continued to have linkages and collaboration with other Hospital committees.

SPECIAL PROJECT: ISSUANCE OF RADIO-ISOTOPES PRODUCTION LICENSE

The practice license of Radio-Isotopes Production was issued by KACST in favor of the new PET cyclotron facility of Cyclotron & Radiopharmaceuticals Department. This is the first national license of its kind. The construction phase and installation of the new "baby" PET cyclotron was finished in 2007. The RSO was given the lead role in preparation for its licensing. The RSO has supervised the final phase before operation and assured that the facility has met the national requirements and standards by communicating with KACST. The safety measures were all evaluated to ensure compliance with national regulatory requirements for radiation safety during emergencies.

Secondary Standard Dosimetry Laboratory

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

Head of Unit:

M. Gary Sayed, PhD

Members:

Abdalla Al-Haj, PhD

Nabil I'Qilan, MSc

Rana Al-Qwiz, BSc

Amal Al-Mutairi (RC Grant)

ACTIVITIES

For the year 2008, 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 (Figure 1). A total of 628 radiation-measuring instruments were calibrated, inter-compared and acceptance tested. These instruments include 607 survey meters, 12 pocket dosimeters, 2 radiotherapy

dosimeters and 7 diagnostic dosimeters (Figure 2). A total of 144 quality control tests of counting systems were performed. It has also provided irradiation services for the quality control test of TLD readers of service providers in the Kingdom where a total of 52 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.

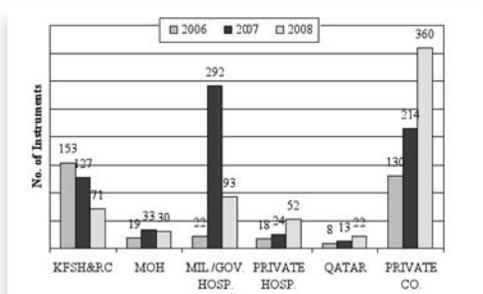


Figure 1. Graph showing the calibration services provided by the SSDL to different departments of KFSHRC as well as other institutions.

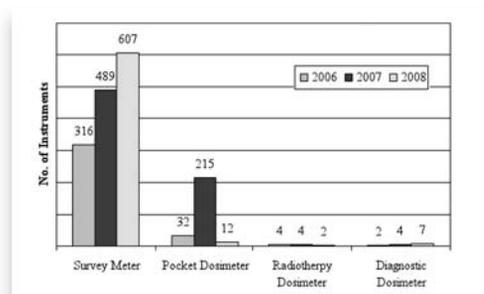


Figure 1. Graph showing the number of external facilities served by the SSDL in year 2008.

THE DEPARTMENT OF
BIostatISTICS EPIDEMIOLOGY &
SCIENTIFIC COMPUTING

The Department of Biostatistics, Epidemiology, & Scientific Computing

The year 2008 has been a year of accomplishments for the Department of Biostatistics and Epidemiology. The most significant contributions are tremendous effort made by the Epidemiology Research Unit to host the 7th 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 provides users support on many technical issues. Its members 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 analysis of biomedical data.

Organizationally, the Department is structured into six groups – biostatistics, epidemiology, computing services, registries, technical databases and administrative services. The first two of these are the primary generators of original research, and the latter four are support core facilities.

This report presents the accomplishments of the various groups in terms of the research and information technology projects on which the respective participated. Some research projects are internally driven by the Department’s staff, and some are directed by investigators outside the Department. Project-based research is the fundamental process through which we function as a Department. Programming and developments of data bases for clients outside the King Faisal Specialist Hospital is a new venture that our Technical Data Base are charged with. During the year well over 40

Chairman:

Mohamed Shoukri, PhD

Administrative Support Staff

Cielo Dupaya-Mendiola

Ismail El Sayed S. Mohammed

Alia Gabr

Abel Pangilinan

projects were registered by the Department. The work resulted in books, publications, presentations, workshops and symposia. Associated with each project listed in this report is a statement as to the product resulting from the efforts of Departmental staff working on the project.

In comparison to 2007, our productivity has been at par with the past. The number of staff has decreased in the past year due to several resignations. However, despite that, the publication rate has maintained its level. We continue to aim for higher impact publications, and to that end believe that we have been particularly successful. Also, despite the decrease in the number of staff, the core facilities have continued to maintain their support of important projects, e.g. the provision of high quality computing services, the accurate collection of patient data on ten disease registries and the development and enhancements to technical databases, the management

of gigabytes of research data for ever increasingly complex research projects, the often-customized analysis of genetic data, and the efficient provision of administrative support to a research department.

We look forward to the year 2009 as a transitional year when new initiatives will be pursued and other initiatives suspended – of special note are increased sophistication into epidemiological studies, the focus on the registries and developing strategies for long-term support thereof and the applications of computational statistics and its application in the analysis of micro-array gene expressions data. The Department plans to establish the national birth defect registry with support from Prince Salman Centre for Disability Research. Our base of support provided to Hospital Administration is now wider and we expect to be an important partner in the Data Warehouse Project.

Biostatistics Research Unit

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 the 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.

OUR PRINCIPLES ARE SUMMARIZED IN

Excellence: We set high standards for the recruitment and performance of our staff. This is our approach to achieve excellence in research. **Selectivity:** We shall identify our strengths and build on them with selective allocation of resources. **Responsibility:** Through our services to the scientific community, we aspire to play a significant role in improving the quality of medical research and hence the quality of life of patients. **Accountability:** We are accountable to the Administration of the Research Centre for the quality of our research, our teachings, and services to the scientific community and for the use of our valuable resources. **Partnership:** We seek cooperative relationship with other institutions and government organizations in the Kingdom of Saudi Arabia to enhance and support research and educational opportunities.

Head of Unit:

Mohamed Shoukri, PhD

Members:

Naser Elkum, PhD

Gamal Mohamed, PhD (three months)

Dilek Colak, PhD

Salah Al Gain, MSc

Abdelmoneim Eldali, MSc

Samia Al Hashim, BSc

Wilhelmina Ventura, BSc

RESEARCH PROJECTS

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

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

There are two competing designs under which BE can be investigated; the first being the parallel-groups design and the other is the crossover design. For both designs, the methodologies for establishing equivalence have focused on the application of Feiller's theorem (1954) for the normal data and the likelihood ratio test for categorical data. In this project we shall use an entirely different technique for inference. The theoretical underpinning of this approach was developed by Neyman (1937) and later extended by Moran (1973). The approach was termed by them "the τ " 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. A final report has been submitted to ORA.

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 to 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.

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 (combine 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. A final report has been submitted to ORA.

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 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.

Project Title: Factors Influencing Outcome of Acute Illnesses Associated With the Length of Waiting Time in the Emergency Room at KFSH&RC, RAC# 2031044.

Primary Investigators: N. Elkum, A. Al-Madouj

Co-Investigators: M. Shoukri

PROJECT DESCRIPTION

A Prolonged waits in the emergency room (ER) before being seen by a doctor may influence the outcome of an acute illness. Moreover, the longer the waiting time the higher the chance that a patient will leave the ER regardless of the severity of his/her illness, a known state referred to in the medical records as "Left without seen" or "LWS". Preliminary investigation showed that the rate of balking of patients in ER is high at KFSH&RC. In this project we plan to investigate the waiting time for patients who come to the ER and identify factors that may cause slowing in the process of patient's admission.

PROGRESS

The project has been successfully completed and a paper has been accepted for publication.

Project Title: Cellular and Molecular Characterization of Medulloblastoma in Saudi Patients: Correlation With Prognosis and Therapy, RAC# 2050 016.

Primary Investigator: A. Abousekhra

Co-Investigator: N. 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. 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.

Project Title: Efficacy of Peginterferon α -2a in HBeAg Negative Chronic Hepatitis B: Naïve versus Lamivudine Resistance Patients, RAC# 2051045.

Primary 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 α -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

RAC approved this project and has been approved to be funded by Pharmaceuticals Hoffmann- La ROCHE (SR 1,000,000.00).

Project Title: Knowledge and awareness about cancer and its prevention: Attitude towards Cancer Preventive Health Behaviour, RAC# 2051041, KACST# MS 11-1.

Principal Investigator: K. Ravichandran

Co-Investigators: G. E. Mohamed, N. Al Hamdan, A. 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. Preparation to start data collection is underway.

Project Title: Selenium Status in Adults and Children of Different Ages Living in Al Kharj Area and Its Possible Relationship With Common Endemic Diseases, RAC# 2020009.

Principal Investigator: I. Al-Saleh (BMR)

Co-Investigators: G. Mohamed, A. A. Hogah (Primary Health Care Unites, Al Karj, MOH)

PROJECT DESCRIPTION

Selenium is an essential element, cofactor for glutathione peroxidase activity whose deficiency may induce modification in the cellular antioxidative status and induce the appearance of different diseases. Studies suggest that a serum selenium concentration of 0.045 µg/ml may correlate with an increased risk of coronary heart diseases, coronary atherosclerosis and cancer. The selenium content of the soil determines its concentration in the food chain, which in turn determines the regional nutritional selenium status. Previous studies by the principal investigator in Al-Kharj Province reported low selenium levels in the soil of 3 dairy farms and the milk of lactating mothers living in that region. This could be a public health problem and research is needed to determine the magnitude of the problem in specific areas in Saudi Arabia and to identify the factors that should be taken into consideration for prevention. Generally, selenium functions as an antioxidant that works in

conjunction with vitamin E. A cross-sectional study will be conducted among Saudi children and adults attending the Primary Health Care Units in Al-Kharj Province. In order to assess the selenium and vitamin E status and its association between DNA damage and antioxidant status. Serum and fingernail samples will be collected for this study.

PROGRESS

This project was approved by KACST. Data analysis has been completed. A manuscript has been published in *Clin Chim Acta*.

Project Title: DNA Damage due to Polycyclic Aromatic Hydrocarbons Exposure among Colon Cancer Patients and Its Possible Role in Inducing Carcinogenesis, RAC# 2020014.

Primary Investigator: I. Al-Saleh (BMR)

Co-Investigators: G. E. Mohamed, J. Arif (BMR), N. Al Sanea (Surgery), A. Abdul Jabbar (Surgery)

PROJECT DESCRIPTION

Colon cancer represents 4.9% of all tumors at KFSH&RC. Environmental factors have long been suspected to play a prominent role in colon cancer etiology. Human exposure to polycyclic aromatic hydrocarbons (PAHs) and other carcinogens can be due to occupational, environmental and dietary sources. Among the PAHs, benzo(a)pyrene (BP) is a potent carcinogen. It metabolizes to the ultimate reactive form, BP-diol-epoxide (BPDE) binds covalently with DNA to form BPDE-DNA adducts. These adducts, if they are not repaired or are misrepaired, may initiate gene mutations and lead to cancer. The high consumption of grilled meat and similarly the smoking prevalence in our community in Saudi Arabia could be potential factors in the incidence of colon cancer among Saudis. This has lead us to design this comparative study in order to quantify the exposure to BP and other carcinogens measuring DNA-adducts in colon tissues and evaluate its role in the etiology of colon cancer. Furthermore, BP in serum and urinary 1-hydroxypyrene (as a major pyrene metabolite),

will be determined as an indicator of individual's internal dose of PAHs

PROGRESS

Data collection and analysis completed. A manuscript will be submitted for publication.

Project Title: Prevalence of Anemia and the Transfusion Practices in Critically Ill Patients, RAC# 2031018.

Primary Investigators: K. Al Maghrabi (Medicine)

Co-Principal Investigator: R. Al Hubail (Medicine)

Co-Investigators: G. Mohammed, M.Hijazi (Medicine), N.Abouchala (Medicine), T. Wetterberg (Medicine)

PROJECT DESCRIPTION

Anemia is common in the critically ill patients. By day 3 of intensive care units (ICU) admission, ~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 re-evaluation of the clinical practices of blood transfusion and blood conservation. The transfusion practice in the 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 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 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 product, which carry a great importance in the presence of donor shortage and variable multiple risks associated with transfusion.

PROGRESS

Approved by RAC. Data collection and data entry is going on.

Project Title: The Use of Chlorhexidine Oral Care for the Prevention of Ventilator Associated Pneumonia, RAC# 2021076.

Primary Investigators: M. Hijazi (Medicine)

Co-Investigators: G. Mohammed, K.Al Maghrabi (Medicine), R. Al Hubail (Medicine), N. Abouchala (Medicine), T. Wetterberg (Medicine)

PROJECT DESCRIPTION

This is a prospective, randomized, double blind, clinical trial to compare oral care using chlorhexidine with the routine oral care on the occurrence of Ventilator-Associated Pneumonia (VAP) in mechanically ventilated medical and surgical critically ill patients. The study is to be conducted at 28 beds medical-surgical ICU of KFSHRC which is a tertiary care hospital. The primary endpoint is the occurrence of VAP. Secondary endpoints are mechanical ventilation days, ICU stay and ICU mortality. All patients aged 14 and more requiring mechanical ventilation for > 24 hours will be eligible for inclusion in this study. Those who are known to have hypersensitivity to Chlorhexidine gluconate, or admitted with a diagnosis of pneumonia and inability to perform oral care for any reason are excluded.

PROGRESS

Data collection in progress. More than 228 patients were recruited to this date (equal number each treatment arm).

Project Title: The Role of Positron Emission Tomography (PET-FDG) in the Initial Evaluation and Long-Term Prognosis of Differentiated Thyroid Cancer, RAC#2031 025.

Primary Investigator: A. Alzahrani

Co-Investigators: G. Mohamed, S. Bakheet (Medicine), S. Al Sobhi (Surgery), S. Salam (Medicine)

PROJECT DESCRIPTION

Positron Emission Tomography (PET) is a relatively new imaging modality. Its role in differentiated thyroid cancer (DTC) and other types of cancers is being explored. Previous studies have shown its promising role in the follow-up of patients with DTC. No study however has assessed its potential role in the initial evaluation of patients with DTC. King Faisal Specialist Hospital is the major referral center for the management of DTC. Currently, more than 2,500 patients are on long-term follow-up and about 100-150 new cases are seen annually. Unfortunately, most of the newly referred cases have had inadequate surgical procedure at their local hospitals. Partial thyroidectomy has been associated with increased risk of long-term recurrence and mortality from DTC. Others and we have shown a high prevalence of residual thyroid cancer in the residual thyroid tissue and cervical lymph nodes, which are resected at completion thyroidectomy. It is mainly this high prevalence of residual thyroid cancer that led to recommendation of near total or total thyroidectomy by most experts and endocrine bodies as a standard surgery for the vast majority of patients with DTC. If one can identify with high accuracy those patients who still harbor residual malignancy after partial thyroidectomy, then one may be more selective in choosing patients for completion thyroidectomy. Unfortunately, current diagnostic methods lack such a high accuracy to differentiate those patients with residual malignancy, who should undergo completion thyroidectomy, from those who do not have residual DTC and therefore may not need further surgery. Obviously, such an accurate diagnostic test would have significant therapeutic and cost-effective implications.

PROGRESS

An abstract was submitted to the endocrine society's 88th annual meeting, June 2006, Boston Convention centre.

Project Title: Longitudinal Study of Prenatal and Postnatal Lead Exposure and Early Cognitive Development in Al Kharj, Saudi Arabia, RAC# 2031050.

Primary Investigator: I. Al-Saleh (BMR)

Co-Investigators: G. Mohamed, S. Schroeder (PSCDR), A. Rabah (Pediatrics, King Khalid Hospital)

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 10th percentile, medium lead exposure risk group (at approximately 50th percentile) and high lead exposure risk group (above the 90th percentile). Development will be assessed semiannually, 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. Statistical analysis is underway.

Project Title: Weaning of Patients With Tracheostomy using Intermittent Trachmask at Trachmask at Preset Duration or Extended Trachmask as long as Tolerated (Prospective Randomized Trial), RAC# 2021074.

Primary Investigators: M. Hijazi (Medicine)

Co-Investigators: G. Mohammed, K. Al Maghrabi (Medicine), N. Abouchala (Medicine), T. Wetterberg (Medicine)

PROJECT DESCRIPTION

Most patients who require invasive mechanical ventilation (MV) can be liberated quickly from the ventilator after resolution of the acute precipitating illness, but a significant population fails multiple weaning attempts and requires prolonged mechanical ventilation (PMV). Approximately 20% of patients in the critical care setting will need PMV defined as >21 days of MV (definition of the health care financing administration).

Tracheostomy is commonly performed for patients anticipated to need PMV. It improves patients comfort, facilitates more effective suctioning, decreases airway resistance, enhances patients mobility, increases opportunities for articulated speech and the ability to eat orally. Moreover, it provides more secure airway that can be used intermittently for weaning.

PROGRESS

Approved by RAC.

Project Title: Exposure to Environmental Pollutants and Its Effect on the Outcome of In-Vitro Fertilization Treatment, RAC# 2010006

Primary Investigators: I. Al-Saleh (BMR)

Co-Investigators: G. Mohamed, S. Coskun (Pathology), K. Jaroudi (Obstetrics and Gynecology)

PROJECT DESCRIPTION

Published data indicate that chemical exposure to heavy metals, organic solvents, pesticides, endocrine disruptors and smoking may cause alterations in reproductive system and contribute to sub fecundity, infertility, pregnancy loss, growth retardation, intrauterine fetal demise, birth defect and ovarian failure in laboratory and wildlife. The mechanism by which chemicals alter reproductive function in all species is complex and may involve hormonal and/or immune disruption, DNA adducts formation, altered cellular proliferation, or inappropriate cellular death. Previous studies revealed that Saudi population could be exposed to lead, mercury, cadmium, pesticides and smoking products through different sources. This prospective study is designed to look for possible associations between exposure to lead, cadmium, mercury, smoking, DDT and its metabolites among Saudi women undergoing IVF program and infertility and whether it has an influence on the treatment outcome. Environmental pollutants will be detected in follicular fluids and blood samples collected from participants using Gas Chromatography with Mass Spectroscopy, High-Performance Liquid Chromatography and Atomic Absorption Spectrometry.

PROGRESS

Data collection in the final stage.

Project Title: Hunting for one of the Autism Genes that Might be Linked to Osteopetrosis With Renal Tubular Acidosis. PSCDR 02-R-0029-NE-02-AU-1, RAC # 2030-046.

Investigators: Kaya N, Ozand P, Al-Odaib A, Colak D, Meyer B, Sakati N, Nester M

PROJECT DESCRIPTION

This proposal is to investigate patients with osteopetrosis and renal tubular acidosis with autism. A region where carbonic anhydrase 2, the deficient protein in osteopetrosis and renal tubular acidosis is centered will be studied for (a) polymorphic markers using Affymetrix high density SNP chips B) carbonic anhydrase 2 gene

mutations; 3) for possible inversion within the region or 4) for possible microdeletion in the region, 5) global gene expression profiling using Affymetrix's GeneChips. It is anticipated that a gene or genes linked to autism will be thus identified, differences in phenotype will be determined based on gene expression studies and these results should contribute to the research on autism-associated gene markers.

PROGRESS

The whole-genome mRNA expression profile in lymphoblastoid cells from 30 consented patients were performed by utilizing Affymetrix GeneChip Human Genome U133 Plus 2.0 gene expression arrays. The mutation analysis on CA2 gene is performed and confirmed the presence of mutation in the patients. Gene expression signatures were found using several statistical and bioinformatics techniques for each disease subtype (OPRTA patients with normal intelligence, OPRTA patients with mental retardation, OPRTA patients with autism). To the best of our knowledge, our gene expression study is the first study for OPRTA and points out novel pathways for different subtypes of OPRTA. Our results will help better understand genetic underpinning of this complex disease and its association with mental retardation (MR) and autism. The project is finalized, one manuscript is under preparation, the research findings were presented at The Pacific Symposium on Biocomputing, Big Island of Hawaii, 2009, and at the Annual Research Day, KFSHRC, 2009.

Project Title: Molecular Genetic Studies in Chromosome Disorders, RAC #2040 042.

Investigators: Kaya N, Colak D, Owain M, Sakati N, Al-Odaib A, Al-Dosari N, Walter C, Hasnen Z

PROJECT DESCRIPTION

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

PROGRESS

We have collected samples from patients (mainly children) based on our inclusion criteria. We performed high-resolution aCGH using Agilent high-density chips, linkage, CNV, and genome-wide gene expression studies using Affymetrix GeneChip SNP and gene expression assays. We performed the data analysis and obtained initial results. We are currently confirming our results and investigating the allelic frequencies of these CNVs in the Saudi population. We are also in the process of targeting and sequencing the candidate genes from the genome-wide scan analysis, and identify genes or groups of genes underlying the dysmorphic syndromes. One poster were presented in Human Genome Variation Meeting in September 2007, Barcelona, Spain and published in Proceedings of the 9th International Meeting on Human Genome Variation and Complex Genome Analysis, and another poster was presented at the Annual Research Day, KFSHRC, 2008, and multiple manuscripts are under preparation.

Project Title: Molecular Characterization of Autism Spectrum Diseases: A Pilot Study for Three Distinct Disorders, RAC # 2040 024.

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

PROJECT DESCRIPTION

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

denominator(s) can be detected. This approach will help to establish a link between genetic alterations and gene signatures within and among the diseases of interest.

PROGRESS

We have performed gene expression profiling using Affymetrix's Human HG-U133 Plus 2.0 gene expression chips on whole blood RNA from patients and sex and age matching controls. We have identified genes that are common among the autism spectrum diseases. The Principle Components analysis as well as hierarchical clustering clearly classified individuals based on their genetic etiology. Genotyping and mutation screening studies were performed and a novel mutation was found for OPRTA. A manuscript is under preparation.

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. The gene signatures in whole blood and identification of key genes likely to participate in the apoptotic and nuclear / mitochondrial dialogue for this disease will be performed using ABI 1700 Microarray system. Linkage experiments as well as fine mapping experiments will also be performed on familial cases.

PROGRESS

We have collected blood from nine patients from different parts of Saudi Arabia. Global gene expression profiling was performed on patients and age and sex matching controls using ABI 1700 system. Initial data analysis was performed by using several statistical and bioinformatics tools. The differentially expressed genes

in patients compared to controls have been determined with statistical significance. The unsupervised analysis clearly separated individuals based on their subject group. Functional annotation and biological term enrichment analysis were performed. Also, Linkage studies were performed on familial cases and currently fine mapping and sequencing of targeted genes are ongoing. One poster presented at the Annual Research Day, KFSHRC 2008, and a manuscript is under preparation.

Project Title: Gene Expression and Immunohistological Finding in Patients With Papillion Lefevre Syndrome, RAC# 2070022.

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

PROJECT DESCRIPTION

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

PROGRESS

We are in the process of collecting samples.

Project Title: Proteomic Analysis of Human Breast Cancer Stem Cells/Progenitor Cells, RAC # 2080021.

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

PROJECT DESCRIPTION

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

PROGRESS

The project was recently approved by RAC.

Project Title: Identification of Environmental and Genetic Factors that Influence Breast cancer development and therapy in Saudi Females, RAC# 2031091.

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

PROJECT DESCRIPTION

Breast Cancer is the major cause of morbidity and mortality among females in Saudi Arabia. Clinical observations indicate that the breast cancer developed before the age 40 accounts for 26.4% of all female breast cancers in Saudi Arabia as compared with only 6.5% in USA. Breast cancer in young Saudi females is more aggressive in nature with poor prognosis and disease free survival. Thus new diagnostics, prognostic and therapeutic markers are needed. We conducted a comprehensive analysis of global gene expression changes to characterize the underlying biological mechanisms of young age breast cancer in Saudi Arabia. We also investigated gene expression profiles of cancer progression from normal to preinvasive stage of ductal carcinoma in situ (DCIS) and to potentially lethal stage of invasive ductal carcinoma (IDC).

PROGRESS

We analyzed the whole-genome mRNA expression profile from tumor and adjacent disease free tissues of 115 samples using Affymetrix GeneChip Human Genome U133 Plus 2.0 Arrays. Both unsupervised and supervised analyses were performed. We have found 1756 genes as differentially expressed between patients compared to normal controls (adjusted p value <0.05 and fold change >2). The hierarchical clustering as well as principle component analysis (PCA) clearly separated individuals as either patients or normal controls. We have identified age-specific tumor signature genes for very young age (age < 35) and two mature groups. Functional and pathway analysis revealed some distinct and shared functional categories and pathways among three age subgroups. Our initial results on cancer progression revealed that there are most changes occur between normal to IDC, with relatively smaller list of differentially expressed genes distinguishing DCIS from normal. Further investigation of this list is warranted because it potentially contains the key genes as well as the pathways that they are involved and are important in the transformation from DCIS to IDC breast cancer.

Project Title: Mitral Balloon Valvotomy – Immediate and Long Term Effect. BESC #: 011/1995.

Primary Investigator: Mohammed Fawzi, MD

BRU I: Abdelmoneim Eldali

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: Coagulation and Fibrinolysis Responses Pattern to Severe Heatstroke and its Relation to Inflammation and Cell Injury in Baboon Model: Effects of Tissue Factor Neutralization on Outcome, RAC #: 2050 012.

Primary Investigator: Abderrezak Bouchama, MD

BRU I: Abdelmoneim Eldali

DESCRIPTION

Heatstroke is a public health problem when the pilgrimage to Makkah in Saudi Arabia enters in the hot cycle of the year. For instance, in August 1985, of the 2000 cases of heatstroke that were reported within a week, more than 1000 were fatal. Heatstroke causes multiple organ injury that can culminate in death despite cooling and intensive care management. It is clear now that better cooling techniques will not improve outcome; a new treatment, evolved from a better understanding of the pathophysiology of the disorder, is needed. Heatstroke is associated with massive activation of coagulation and inflammation leading to microvascular damage and thrombosis in various organs, and death. Knowledge of the time course and pattern of coagulation and inflammation in heatstroke is important for the development of new modalities of treatment. Using a baboon model of heatstroke, we propose to evaluate the coagulation response to heatstroke and its relation to inflammation and tissue injury. In a second step, we will test the hypothesis that inhibition of coagulation and inflammation using inactivated factor VII can prevent tissue injury and reduces the lethal effects of heatstroke.

PROGRESS

In the data analysis phase. Several publications and presentations resulted from this project.

Project Title: Signaling Pathways Involved in Heatstroke Pathogenesis, RAC #: 2060 013.

Primary Investigator: Mohammed Dehbi, PhD

BRU I: Abdelmoneim Eldali, MSc

DESCRIPTION

Cell survival and integrity are fundamental processes that rely on a series of complex transcriptional, translational and post-translational networks to execute their tasks in a coordinated fashion. Aberrant expression or activity of genes involved in these hierarchies often leads to severe clinical manifestations and pathological disorders such as in the case of heatstroke and sepsis. These two distinct pathological diseases share in common similar clinical manifestations such as increased production of pro-inflammatory cytokines, tissue injury, coagulopathy and death.

Most of the organs targeted by heatstroke play a vital role for the organism. They include the brain, heart, kidney, lung and liver, highlighting thus, the severity of heatstroke disease and the vulnerability of these organs. Recent evidence from rodents and baboons suggests that inflammation plays an important pathogenic role in heatstroke.

Sepsis is another systemic inflammatory response due to microbial infection, particularly to specific microbial components such as the endotoxin lipopolysaccharide (LPS). Severe cases of sepsis are characterized by multiple organ injury, coagulopathy, apoptosis and death.

Interestingly, LPS has been shown to enter the circulation of patients with heatstroke and also in animal models of heatstroke. 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.

The specific objectives of this proposal will be achieved as follow:

- Development of an in-house mouse model of heatstroke.
- To examine the heatstroke effect on an endotoxin resistant mouse model.

- Investigate the activation and/or the role of HMGB1 protein in heatstroke response.

Elucidate the nature of the downstream signaling pathways, particularly the TLR-4, involved in heatstroke.

Should these initial experiments begin to help understanding and establishing the hierarchical gene network involved in heatstroke, they will be a valuable tool for identifying novel therapeutic targets for treatment and management of heatstroke.

PROGRESS

In the data analysis phase.

Project Title: Genomic and Proteomic Profiling of Heatstroke in a Mouse Model, RAC #: 2070 015

Primary Investigator: Mohammed Dehbi, PhD

BRU I: Abdelmoneim Eldali, MSc

DESCRIPTION

Heatstroke is a life-threatening condition, particularly in hot countries as well as during heat waves in temperate climate. With the current global warming alert of the planet, and the recent prediction of frequency and severity of the next series of heat waves, this disease has emerged as a serious medical problem worldwide. For example, during the recent European heat wave of August 2003, there were at least 45000 victims of heat injury that succumbed immediately within a two weeks period. Clinically, heatstroke is characterized by an increased body temperature to above 41°C, massive disseminated intravascular coagulation (DIC), excessive inflammatory response and multiple tissue injuries that culminate into death. Despite optimal cooling and supportive treatment, the mortality and neurological morbidity associated with heatstroke remain significantly high. Therefore, there is an urgent need to develop novel preventive and/or therapeutic strategies. For this purpose, the pathogenesis of heatstroke and factors underlying the progression from heat stress to heatstroke would need to be unraveled.

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.

PROGRESS

In the data analysis phase.

Project Title: Gulf Center for Cancer Registration, RAC# 2061 022, BESC# 002/2006.

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

PROJECT DESCRIPTION

The Gulf Center for Cancer Registration (GCCR) was established in 1997. The GCCR database, population-based incidence data that include information on both benign and malignant primary tumors, is of the largest aggregations in Asia. Data is compiled from the six national cancer registries representing the six Gulf countries: Kingdom of Bahrain, Kingdom of Saudi Arabia, State 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.

PROGRESS

The population pyramid for each GCC country was produced in SAS[®] for the GCCR Annual/Cumulative Report. An additional population tree was created to represent ALL GCC countries. Seven new programs were written in SAS to produce seven population trees for seven different age groups; each age group displaying the top ten incidences of cancer in both males and females in Saudi Arabia. Interactive population tree charts were generated, as well

Project Title: Pan Arab Liver Transplantation Registry, RAC# 2071 022, BESC# 003/2007.

Investigators: Al Sebayel M, Khalaf H, Alawi K, Mahmoud S, Shoukri M, Subhani S, Hashim S

PROJECT DESCRIPTION

In March 2006, the Pan Arab Liver Transplantation Society (PALTS) was established. One of their goals is to establish a web-based registry for the Pan Arab Liver Transplantation that will help promote and encourage education, research and cooperation in the field of liver transplantation among the different liver transplant programs in the Arab world. Based on epidemiological studies done in the Kingdom since the early '80s, it is estimated that the prevalence of viral hepatitis is around 10% making Saudi Arabia one of the endemic areas of liver disease world wide. Moreover, it is known that hepatocellular carcinoma is the most common malignancy among young Saudi males. It has been estimated that between 500-700 patients need a liver transplant done annually. The main objective of this study is to monitor the liver transplantation activities in KFSH&RC and in the Arab world, and to aim for better follow-up and care for post liver transplant patients. In addition, the web-based registry will help in estimating the need of liver transplantation in both the Hospital and in the Arab world.

PROGRESS

Both data analysis and presentation for this project have been done in SAS for the purpose of generating the PALTR Annual/Cumulative Report. Additional statistical analysis was done to produce a number of survival curves.

Project Title: Thromboembolic Disorders Registry, RAC# 2001 045, BESC# 004/2001.

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

PROJECT DESCRIPTION

The Thromboembolic Disorders Registry of King Faisal Specialist Hospital 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.

OBJECTIVES

1. Data resource that could assist the health care to evaluate the results of their therapeutic effort and analyze reasons for complication like the Thromboembolic episodes or Bleeding disorders occurring during Anticoagulation Therapy.
2. To provide leadership in establishing and maintaining comprehensive TED Registry in collaboration with other National Organization.
3. Serve as database for future research.
4. Data resource could enable us to improve some methods of prophylaxis of DVT and standardize the recommended regimens for prophylaxis, which could lead to improvement of the approaches to prevention.
5. Enable stratification of patients into different risk groups.

PROGRESS

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

Project Title: Cleft Lip/Palate and Craniofacial Anomalies Registry, RAC# 991 030, BESC# 007/1999.

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

PROJECT DESCRIPTION

The Cleft Lip and Palate (CLP) registry was established in 1999. The purpose of this study is to provide a database on cleft lip/cleft palate patients at

KFSH&RC. CLP are one of the most common human malformations and the most common malformation of the face. CLP is a complex and chronic disability lasting from birth through adulthood. The objective of this study is to determine the type and prevalence of CLP in the KFSH&RC population. In addition, the data will contribute information for reporting, conducting research studies and health care planning.

PROGRESS

SAS programs have been written for data analysis and presentation for the CLPR Annual/ Cumulative Report, and for the publishing of some research papers.

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

Both data analysis and presentation for this project have been done in SAS[®] for the purpose of generating the

Epilepsy Registry Annual/Cumulative Report. 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 to determine the types of neuromuscular diseases found in the population. Moreover, to obtain patterns of these diseases at KFSH&RC, identify associated risk factors, and to document diagnostic and treatment procedures. This registry is prospective with no sex, nationality, or age exclusion criteria.

PROGRESS

Both data analysis and presentation for this project have been done in SAS[®] for the purpose of generating the NMDR Annual/Cumulative Report. Technical support was provided when needed.

Project Title: Congenital Heart Disease Registry, RAC# 991 026, BESC# 011/1996.

Investigators: Al Mohanna F, Shoukri M, Canver C, Al Yousef

S, Momenah T, Joufan M, Al Halees Z, Omrani A, Subhani S, Al Firm A, Dessouky N, Bawayn N, Barhoush L, Khalil H, Marzouky M, Al Zahrani A, Hashim S

PROJECT DESCRIPTION

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

PROGRESS

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

Project Title: Neural Tube Defects Registry, RAC# 991 029, BECS# 018/1999.

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

PROJECT DESCRIPTION

Neural Tube Defects (NTD) are serious birth defects with symptoms that range from mild to severe degrees. They are a group of birth defects, which have a

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

PROGRESS

Both data analysis and presentation for this project have been done in SAS[®] for the purpose of generating the NTDR Annual/Cumulative Report. Technical support was 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 rates. 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.

PROGRES

Both data analysis and presentation for this project have been done in SAS[®] for the purpose of generating the NDR Annual/Cumulative Report. Technical support was provided when needed.

PUBLICATIONS

REFEREED PAPERS

- ↪ Shoukri, M.M. and Donner, Bivariate modeling of inter-observer agreement coefficient. *Statistics in Medicine*; 28:430-440, 2009 .
- ↪ Fawzy, M E, Shoukri, M.M., Fadel, B., Badr, A., Al Ghamdi A., Canver, C. Long-Term (up to 18 years) clinical and echocardiographic results of Mitral Balloon Valvuloplasty in 531 consecutive patients and predictors of outcome. *Cardiology*, 113: 213-221, 2009.
- ↪ Ahmed, M. and Shoukri, M M. A Bayesian estimator of the intra-class correlation coefficient in beta-binomial sampling. *Journal of Data Science*. 2009. In press.
- ↪ El-Kum and Shoukri. M.M. Signal to noise ratio (SNR) as a measure of reproducibility: design, estimation, and application. *Health Services and Outcome Research Methodology*, Vol. 8, No. 3 119-133, 2008.
- ↪ Shoukri, M.M., Colak, D., Kaya, N., and Donner, A. Comparison of two dependent within subject coefficient of variation to evaluate the reproducibility of measurement devices. *BMC Medical Research Methodology*, 8:24 1-11, 2008.
- ↪ Kumar, P. and Shoukri, M.M. Evaluating aortic stenosis using the Archimedean copula methodology. *Journal of Data Science*, 6, 1-18 2008.
- ↪ Fawzy, M., Shoukri, M. M., Osman, A., El-Amraoui, S., Shah, S., Nowayhed, O., and Canver, C. Impact of atrial fibrillation on immediate and long term results of mitral balloon valvuloplasty in 531 consecutive patients. *Journal of Heart and Valve Disease*, Vol. 17 (2), 141-148, 2008.
- ↪ Mourad, W., Al-Thani, S., Tbakhi, A., Al-Omari, M., Khafaga, Y., Shoukri, M.M. El-Wishi, A., Al-Shabana, M., Ezzat, A. Morphologic, immunphenotypic and clinical discriminators between T-cell/ histiocyte-rich large B-cell lymphoma and lymphocyte-predominant Hodgkin Lymphoma. *Hematology Oncology Stem Cell Therapy* 1 (1) 22-27, 2008.
- ↪ N Kaya, D Colak, P Ozand, "Autism spectrum disorders: a review", *Trends in Developmental Biol.* vol. 2, 2008, pp. 71-112.
- ↪ Kaya N, Imtiaz F, Colak D, Al-Sayed M, Al-Odaib A, Al-Zahrani F, Al-Mubarak BR, Al-Owain M, Al-Dhalaan H, Chedrawi A, Al-Hassnan Z, Coskun S, Sakati N, Ozand P, Meyer BF, "Genome-wide gene expression profiling and mutation analysis of Saudi patients with Canavan disease.", *Genet Med.* 2008 Sep;10(9):675-84.
- ↪ Kaya N, Al-Owain M, Albakheet A, Colak D, Al-Odaib A, Imtiaz F, Coskun S, Al-Sayed M, Al-Hassnan Z, Al-Zaidan H, Meyer B, Ozand P, "Array comparative genomic hybridization (aCGH) reveals the largest novel deletion in PCCA found in a Saudi family with propionic acidemia.", *Eur J Med Genet.* 2008 Aug 26.
- ↪ Anas M Alazami, Amr Alsaif, Saeed Bohlega, Abdulaziz Al-Semari, Soumaya Zlitni, Fatema Alzahrani, Prashant Bavi, Namik Kaya, Dilek Colak, Andy Baltus, Borut Peterlin, Sumita Danda, Kailash P Bhatia, Susanne A Schneider, Chris Walsh, Futwan Al-Mohanna, Brian Meyer, Fowzan S Alkuraya, "Mutations in C2orf37, Encoding a Novel Nucleolar Protein, Cause a Multisystemic Disorder of Diabetes, Dystonia, Alopecia and Hypogonadism (Woodhouse-Sakati Syndrome)", *Am J of Hum Genetics*, 2008 Dec;83(6):684-91.
- ↪ D Colak, N Kaya, J Al-Zahrani, P Muiya, E Andres, N Dzimiri, "Left ventricular global transcriptional profiling in human end-stage dilated cardiomyopathy", 2009 (in press, *Genomics*).
- ↪ Mohamed Eid Fawzy, M.D., Miltiadis Stefadourous, M.D., Souad El Amraoui, M.D., Adil Osman, M.D., Iman Ibrahim, M.D., Omar Nowayhed, M.D., Abdelmoneim Eldali, M.Sc., and Charles Canver, M.D. . Long-Term (Up to 17 Years) Clinical and Echocardiographic Results of Mitral Balloon Valvuloplasty in Children in Comparison with Adult Population. *Journal of Interventional Cardiology*, Vol. 21, No. 3, 2008.

- ↔ Mohamed Eid Fawzy, Adil Osman, Vijayaraghavan Nambiar, Omar Nowayhed, Abdelmoneim Eldali, Amr Badr, and Charles Canver. Immediate and Long-Term Results of Mitral Balloon Valvuloplasty in Patients with Severe Pulmonary Hypertension. *Journal of Heart Valve Disease*, Vol. 17, No. 4, September 2008.
- ↔ Abderrezak Bouchama; Corinne Kunzelmann; Mohammed Dehbi; Aaron Kwaasi; Abdelmoneim Eldali; Fatiha Zobairi; Jean-Marie Freyssinet; Dominique de Prost. Recombinant Activated Protein C Attenuates Endothelial Injury and Inhibits Procoagulant Microparticles Release in Baboon Heatstroke. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2008;28:1318.
- ↔ D Colak, N Kaya, J Al-Zahrani, P Muiya, E Andres, N Dzimiri, "Genome-wide gene expression profiling of human end-stage dilated cardiomyopathy using microarrays", accepted for presentation at HDM-2008 International Conference on Multivariate Statistical Modeling & High Dimensional Data Mining, June 2008, Kayseri, Turkey
- ↔ D Colak, MA Chisti, M Goyns, Al Bandery B, MM Shoukri, PT Ozand, N Kaya, "Genome-wide gene expression profiling distinguishes early hepatoma from regenerated (and returned to quiescence) and normal liver in young and old rats", invited talk and published in proceedings of HDM-2008 International Conference on Multivariate Statistical Modeling & High Dimensional Data Mining, June 2008, Kayseri, Turkey.

REFEREED PROCEEDINGS OF MEETINGS

- ↔ D Colak, N Kaya, A BinBakheet, B Alyounes, A Al-Odaib, B Meyer, M Nester, P Ozand, N Sakati, "Molecular analysis of osteopetrosis with renal tubular acidosis (OPRTA) subtypes: Classic OPRTA, OPRTA with autism, and OPRTA with mental retardation", Jan. 2009, The Pacific Symposium on Biocomputing, Big Island of Hawaii, USA.

INVITED PRESENTATION

- ↔ D Colak, MA Chisti, M Goyns, Al Bandery B, MM Shoukri, PT Ozand, N Kaya, "Genome-wide gene expression profiling distinguishes early hepatoma from regenerated (and returned to quiescence) and normal liver in young and old rats", invited talk at HDM-2008 International Conference on Multivariate Statistical Modeling & High Dimensional Data Mining, June 2008, Kayseri, Turkey.

Epidemiology Research Unit

The Epidemiology Research Unit (ERU) within the Department of Biostatistics, Epidemiology and Scientific Computing, is an interdisciplinary research unit, which encompasses a broad range of research specialities. Our mission is dedicated to understanding the patterns and causes of health and disease, and the application of that knowledge in improving the health of populations. The ERU is actively involved in collaborative research with other departments at the KFSH&RC, in addition to external institutions from the region and internationally. Research areas include cancer, cardiovascular disease, mental health, disability, diabetes, child and adolescent health, obesity, nutrition, genetic diseases, and women's health. The ERU currently has 7 scientist staff (4 permanent and 3 adjunct), 5 technical and 2 administrative staff.

The scientists within the ERU have strong links to other institutions and programs, serving as advisors, committee members or collaborating coinvestigators at the International Epidemiological Association, King Saud University, Ministry of Health, King Abdulaziz Medical City, Prince Salman Center for Disability Research, the Executive Board for the GCC States, and Saudi Commission for Health Specialties. Scientists within the ERU are also involved in capacity development through presenting and participating in lectures, seminars and courses on a variety of topics related to epidemiology and research methodology. Our 1st annual Research Methodology course has received excellent reviews and will be instrumental in capacity building of future researchers. ERU scientists have also taught courses at King Saud University and at the King Saud bin Abdulaziz University for Health Sciences. In addition, the unit's staff have supervised several Saudi graduate students, who have benefited from the experience and knowledge of the ERU scientists and their access to ongoing studies.

Head of Unit:

Yasmin Al Twajiri, PhD

Members:

Ali Al Zahrani, MD, PhD

Abdulaziz Al Othaimen, PhD

Ravichandran Kandasamy, PhD

Amal Al Madouj

Batlah Al Murshed

Abdulrahman Bin Muammar

Abdullah Al Joudi, MBBS (Adjunct)

Mansour Al Joufan, MD (Joint Appointment)

Saud Al Shanefey, MD (Joint Appointment)

RESEARCH PROJECTS

Project Title: Epidemiology of Asthma in Mecca and Medina, (RAC# 2081 121).

Investigators: Syed Hasnain, Mohammad Osman Gad-el-Rab, Yasmin Altwajiri

PROJECT DESCRIPTION

Allergic diseases, particularly bronchial asthma and allergic rhinitis, are prevalent in children in Saudi Arabia. The data published internationally has also shown that during the past 10-15 years, bronchial asthma, in school children, has increased to more than double in the Kingdom. Nationally, it stands to about 15% in school age children with regional variations between 12-24%.

Studies conducted under at least two previous KACST funded grants (AR-7-45 and AR 13-45) and completed under KACST publication numbers 86 and 87 dealt directly with the epidemiology and causes of such diseases but remained confined to many major cities without inclusion of the inhabitants of Makkah and Al Madina. Therefore it appears that no allergological, epidemiological, environmental and immunological studies related to asthma and allergic diseases were ever conducted in the two Holy cities except skin prick testing on some individual in Makkah about 15 years ago.

This project, therefore, deals with the allergological aspects including studies of the environmental factors or allergenic profile of both indoor and outdoor environment of the two holy sites, epidemiological study of allergy and asthma in school children, *in vivo* and *in vitro* immunological response in patients of the regions with identified indigenous allergenic factors.

Environmental monitoring and indoor dust analysis of the two sites will be done for at least a 12 month period using state-of-the-art immunoassays with monoclonal antibodies and sampling technology to reveal the antigen's identity, threshold, seasonal and diurnal periodicities, maximum and critical levels of the different allergenic profiles such as house dust mites, animal and insect allergenic proteins (Der p, Der f, Fel d, Per a, Bla g, Bla o Blo t, etc.) present in the indoor environment. Outdoor

environment containing spores from Fungi including molds and mildews (Aspergillus and Cladosporium etc. and non cultivable fungi such as Ganoderma, Coprinus etc. as well as pollen grains from various anemophilous (wind pollinated) plants will be analyzed and identified.

The Epidemiological study will be conducted using a questionnaire, designed by an international panel and used in all previous studies in the Kingdom, in a cross-sectional population of school children, 6-16 years of ages. ISAAC protocol will not be used because of data comparison with previous prevalence study. In addition, ISAAC recruits a limited age - group children for the study which is not our aim in this project.

Based on the findings, a range of allergens will be selected to conduct *in vivo* and *in vitro* immune screening of many allergic and asthmatic individuals. In turn this will help in diagnosis of patients and preparation of an allergen calendar of the regions. This will guide the allergists, chest physicians and health care providers to use the relevant allergens in the diagnostic panel.

PROGRESS

Study proposal has been approved by ORA, and submitted to KACST for funding.

Project Title: Riyadh Puberty Study, (RAC# 2081 020).

Investigators: Alwan I, Felimban N, Altwajiri Y, Shoukri M, Tamimi W, Almutair A, Tamim H

PROJECT DESCRIPTION

There has been a progressive, global decline in the age of onset of puberty during the past century. Improvements in medical care and socioeconomic conditions have been implicated as possible explanations for this change. Age of onset of pubertal characteristics are influenced by genetic, geographic, dietary and socioeconomic factors, however clinicians in Saudi Arabia use Western estimates as standards of reference on the local children, due to lack of country-specific

norms. In addition, puberty has been linked to plasma cholesterol concentration, which is a major risk factor for cardiovascular diseases. The association between plasma cholesterol and sex hormones is not well established, and has been explored by only a few studies. This study will conduct secondary data analysis using existing data, from a representative cross-sectional sample of Riyadh school children and adolescents who were in grades 1 – 10 and who participated in the Riyadh Puberty Study in 2006 (N=1267). Our secondary analysis of this existing dataset will aim at determining and establishing the local standard age of onset of pubertal characteristics and its major influencing factors, among children in Riyadh, Saudi Arabia. The associations between plasma gonadal hormones (LH, FSH, estradiol, and testosterone), plasma lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol) and diet will also be elucidated, adding to the current body of knowledge concerning cardiovascular disease risk prevention.

PROGRESS

1. The secondary data analysis was initiated. Based on the study's inclusion/exclusion criteria the analysis was restricted to children and adolescents ranging in age from 6 – 16 years old. Children with chronic diseases, or who are taking any of the following medications were excluded from the analysis: insulin, cortisone, predinsone, depakin, thyroxine, growth hormone, tegretol, genotropin. Children who met the exclusion criteria were confirmed by the PI (verification using hard-copy questionnaires) before being excluded.
2. Calculating the Design Effect: Due to the complex sampling design used by the original study investigators (cluster sampling), the standard errors are larger than if the sample was a simple random sample of the same size. In order to account for the biased point and variance estimation, the Design Effect had to be calculated for each table produced. Several methods for calculating the Design Effect were tested before the final method was decided upon. Analysis had to be repeated in order to

report estimates which incorporate the Design Effect.

3. The majority of the analysis has been completed. The study investigators have requested from ORA an extension due to the emergence of several important findings during the analysis.

Project Title: Knowledge, Awareness and Attitude About Cancer and Its Prevention, (RAC# 205 1041).

Investigators: K. Ravichandran, G.E. Mohamed, N. 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

Data collection, data entry and data validation were completed. Information from 688 male and 719 female were collected for this study. The mean age of the subjects was 38.5 (S.D. 14.4) years. Only 6.5% were illiterate, 22.4% were at high school level and 33.2% were diploma/university level. 9.6%, 8.2%, 16.6% and 22.6% were unemployed, businessman, administrative staff and housewife, respectively. While 81.2%, 76.1% and 69.4% believe that breast feeding, intake of fruits/vegetables and physical activity, respectively, will not increase the risk of cancer, 47.2% and 24.9% believed fate and curse, respectively, will increase the risk of cancer. About 67.6% not heard any of cancer warning signals and 65.1% listed

TV/Radio as their best source of cancer information. Though 95.8% said early detection is extremely desirable and 76.5% believes early detection prevents all deaths due to cancer, only 55.1% said yes to participate in early detection programme, if any. However 18.2% said likely to participate in such programme. 92.6% felt that their physician recommendation is necessary to participate in such programme. Detailed analysis is in progress; final report and manuscript for a journal will be prepared soon.

Project Title: Cleft Lip/Palate (CL/P) and Craniofacial Anomalies Registry, RAC# 991 030.

Investigators: A. Al-Johar, K. Ravichandran, S. Shazia.

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

Out of the 102 cases registered in 2007, there were 53 (52.0%) male and 49 (48.0%) female with a male to female ratio of 1.08:1. Cleft of lip and/or palate was affected in 64 (62.7%) cases, 22 (21.6%) cases had cranial/facial anomalies and 16 (15.7%) cases had both CL/P and CF anomalies. Out of the 80 cleft cases, there were 43 males and 37 females with the male to female ratio of 1.16: 1. Overall, the soft palate (25; 31.3%) was common followed by bilateral cleft lip and palate (20; 25.0%). Out of the 38 craniofacial anomalies 15 were male and 23 were female, with a sex ratio of 0.65: 1. Twenty one cases (55.3%) had only facial, 10 (26.3%) had only cranial and 7 (18.4%) had both the anomalies.

Except two non-Saudis, one in each gender, all the cases were Saudis. Riyadh region had more number of cases (30; 30.6%) followed by Eastern Province and Al Jouf regions with 12 cases (11.3%) each. No cases were reported from Tabuk region and only one case was outside Saudi Arabia. More than half of the cases parents were not related and 48 cases (47.1%) parents were of first cousin. More than three fourth of the cases (76.5%) has no family history of deformities and only 22 cases (21.5%) have a family history of deformities. Among first cousin 16.7% (8 cases) had familial history whereas among not related 25.9% (14 cases) had family history, which is unusual.

The primary surgeries like Initial lip & nose repair, Initial palate repair accounts to 9.8% and 6.4%, respectively, of the total (358) procedures done. Speech therapy offered to accounts to 7.3% of total procedures. Out of the 35 initial lip & nose repair 15 (42.9%) were done at KFSH&RC and out of 23 initial palate repair 9 (39.1%) were done at KFSH&RC.

A report, 'Cleft Lip/Palate and Craniofacial Anomalies: Annual Report 2007' was published. An article describing the incidence of CLP was published in the peer reviewed journal, *'The Cleft Palate-Craniofacial Journal'*.

Project Title: Prospective Evaluation of Risk-Adapted Therapy for Pediatric Patients With Non-Lymphoblastic Non-Hodgkin Lymphoma (PEDNHL04-1), RAC# 205 1018.

Investigators: A. Belgaumi, A. Al Kofide, R. Sabbah, Y. Khafaga, MA. Iqbal, W. Mourad, K. Ravichandran, K. Siddiqui, L. Osman, Q Al Harbi

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 regimens 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 2008 since 2006.

PUBLICATIONS

- Al Johar A, Ravichandran K, Subhani S. Pattern of cleft lip and palate in hospital-based population in Saudi Arabia: retrospective study. *Cleft Palate Craniofac J*. 2008 Nov; 45(6):592-6.
- Al-Zahrani AS, Ravichandran K, Al-Madouj AN. 2004 Cancer Incidence Report for the Gulf Cooperation Council Countries. Riyadh: Gulf Center for Cancer Registration, 2008.
- Johar AA, Ravichandran K, Subhani SN, Jarba EA. Cleft Lip/ Palate and Craniofacial Anomalies, 2007. King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. March 2008.

Project Title: Burnout syndrome among physicians working in King Faisal Specialist Hospital and Research Centre, RAC# 2081 120.

Primary Investigator: Abdullah Aljoudi

Investigators: Ahmed Hassan (Neuroscience), Mohamed Shoukri (BESC), Yasmin Altwajiri (BESC)

PROJECT DESCRIPTION

Burnout syndrome (ICD-10 Z73.0) is an occupational mental health problem that affects human

service professionals, including physicians, due to chronic job related stresses. It is a syndrome of emotional exhaustion, depersonalization, and reduced personal accomplishment. Studies showed that burnout is a frequent mental health problem among physicians, with rates ranging from 25% to 75%, depending on the working conditions and medical specialty. Its effect can extend beyond physicians, to the services they provide, resulting in lowering the quality of patient care and, in the extreme case, can cause harm to patients. Burnout of physicians can also have indirect economic implications due to high rates of dissatisfaction, absenteeism, turnover and early retirement. The World Health Organization issued a "statement" expressing serious concerns at the increase in the burnout syndrome among physicians, and calling for international research into the causes of this syndrome to develop effective interventions at individual and organizational level. Despite the importance of this occupational mental health problem no study was conducted to investigate burnout among physicians in Saudi Arabia to the best knowledge of investigators. We will estimate the prevalence of burnout and identify the factors associated with it among physicians working in KFSH&RC. We will conduct a cross-sectional study among all physicians working in KFSH&RC using the Maslach Burnout Inventory which is the most validated and commonly used instrument in the world. The SAS program will be used for data entry and analysis. Analyses at univariate, bivariate and multivariate levels will be performed for collected data, to answer the study questions, fulfill the study objectives, report the results and investigate relations between the dependent and the independent variables. Privacy and confidentiality will be safeguarded throughout all phases of the study. The study results will be presented in scientific meetings, symposia and conferences, and will be published in peer-reviewed journals. Results may also be communicated to health policy makers.

PROGRESS

The study has been submitted to ORA and discussed at Clinical Research Committee which request revising of the proposal. The revised proposal has been resubmitted to ORA.

ACTIVE AND ONGOING PROJECTS

1. Principal Investigator: Gulf Center for Cancer Registration: Ongoing project, Ali Al-Zahrani, Kandasamy Ravichandran, Amal Al-Madouj (RAC#: 2061022).
2. Co-Principal Investigator: Arabic Questionnaire for Symptom Assessment used in palliative care, KFSH&RC. Mohammad Al-Shahri, Ali Al-Zahrani, and Mohamed Shoukri (RAC#: 2061049).
3. Co-Investigator: External Pressure Compression for Umbilical Hernia management: Randomized clinical trial. Saud Al-Shanafey, Fahad Al-Hazzani, Abdullah Al-Dowaish, Saleh Al-Olayan, and Ali Al-Zahrani (RAC#: 2071070)
4. Co-Investigator: Survey of Dietary Habits in Saudi Arabia: Katherine Collison, Yasmin Altwajiri, Mohammed Shoukri, and Ali Al-Zahrani.
5. Principal Investigator: Risk Factors for Thyroid Cancer in Saudi Arabia. Ali SA Al-Zahrani, Ali SS Al-Zahrani, Kandasamy Ravichandran, and Naser El Kum. (RAC#: 2081042).
6. Co-Investigator: Use of Antimicrobials during the last week of life in Palliative care unit at KFSH&RC. Mohammed Al-Shaqi, Mohammed Al-Shehri, and Ali Al-Zahrani (RAC#: 2081069).
7. Co-Investigator: Screening for Prevalence and Incidence of Hemophilia A and B Inhibitors among Hemophilic Patients in Saudi Arabia. Tarek Owaidah, Abdul Alkareem Al Momen, Ali Al-Zahrani, et al. (RAC#: 2081007).
8. Co-investigator: Resident-Driven Surgical Training Survey. Saud Al Shanafey, Ali Al-Zahrani (RAC#: 2081100).

Project Title: A Randomized, Open Label, Comparative Evaluation of Conversion from Calcineurin Inhibitors to Sirolimus vs Continued Use of Calcineurin Inhibitors in Renal Allograft BESC# 023/2003, RAC# 2031 054.

Investigator: Abdulrahman Bin Muammar

PROJECT DESCRIPTION

This is a multi-centre international Clinical Trial where KFSH&RC participated in.

Project Title: TyGER study (A Multi-centre, Open-Label, Randomized Comparative Study of Tigecycline vs Ceftriaxone Sodium Plus Metronidazole for the Treatment of Hospitalized Subjects With Complicated Intra-abdominal Infection), BESC# 005/2007, RAC# 2061 076.

Investigator: Abdulrahman Bin Muammar

PROJECT DESCRIPTION

This is a multi-centre international Clinical Trial where I represent KFSH&RC in the investigators meeting in Prague, Czech republic. It is still active and in it's final stages.

PUBLICATIONS

- ↪ Cancer Incidence Among Gulf Cooperation Council States' Nationals - 2004 (Published Monograph by the GCC Executive Board).
- ↪ K. Ravichandran, Al-Zahrani AS. Association of reproductive factors with the incidence of female breast cancer in the GCC Countries. Accepted for publication by the Eastern Mediterranean Health Journal.
- ↪ Surgical Residents' Satisfaction with Current surgical Training Program in Riyadh City. Submitted to the Annals of Saudi Medicine.
- ↪ Cancer Incidence in the GCC State 1998-2005 (in press).

Computing Services Core Facility

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.

Head of Unit:

Parvez A. Siddiqui

Members:

Mashnouf Al-Rowaily

Yousef Hussain

Bandar Al Khodairy

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.

COURSES ATTENDED BY CSCF STAFF MEMBER

Course Name	CSCF staff member
The Seven Habits of Highly Effective People	Mr. Mashnouf
Scholarship	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 2008, CSCF setup new PCs, laptops, workstation, printers, servers and other major computer peripherals. The CSCF was successful in setting up and configuring three new servers with Windows Server 2003 operating software. One of them is called (Al-Haitham) for hosting (CDU-CCC) data. The other one is called Al-Kindi to host RC Users data. The last one is called NFSPREG to host National

Family Safety Program Registry.

CSCF setup and configured 35 new PCs and distributed to assigned departments.

CSCF setup and configured 12 new black and white printers.

CSCF setup and configured 6 color printers.

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

HELPDESK

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

CONFIGURATION AND DISTRIBUTION

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

BMR Molecular Virology and Infectious Diseases: Setup, configured new PCs and also updated old PCs. Installed printers.

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 & laptops.

Department of Biomedical Physics: Setup, configured, installed, and supported PCs, laptops & printers.

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.

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 2008

Department	No. of Logged Calls
BESC	657
BMP	202
BMR	318
CCR	146
CMD	219
CPPEO	49
C&R	101
Genetics	391
ORA	200
RAC-Admin	193
Stem Cell Therapy	251
T&E	70
KNCCCC-Research (CDU)	25
KNCCCC-Research (ADL)	63
KNCCCC-Research (HCGL)	38
Total calls logged	2923

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 2008 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 2008. 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 national and international levels.

Head of Unit:

Shazia Naz Subhani, MSc, Technical Specialist

Members:

Ms. Ahsan Yaseen

Ms. Ehsan El-Shamy

Ms. Najah Aftab Siddiqui

Dr. Nadia Dessouki

Ms. Lina Barhoush

Ms. Nada Bawyan

Ms. Hala Khalil

Ms. Hanaa Abdulghany

Ms. Hala Al Assiry

Ms. Al Gawhara Al Masry

Ms. Ebthisam Al-Jarba

Ms. Mona Hagos

Dr. Rozeena Huma

CURRENT RESEARCH PROJECTS

Research Project: 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, and Dr. Nadia Dessouky

PROJECT DESCRIPTION

The congenital heart defects registry 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 PSSC were prepared and submitted.
- Collaboration with PSSC had been progressive.
- Meetings, Agreements of collaborations and user trainings completed for King Fahad Medical City, Riyadh and Maternity and Children Hospital, Dammam.
- Presentations during King Faisal Heart Institute recognition day.
- Statistics for all year cases as of December 31, 2008 is:

Collaborating Hospitals	New cases	Follow up cases	Diagnosis coding	Treatment coding
(KFSH&RC, PSSC, Dammam Maternity & Children Hospital)	16885	33459	13028	13924

- Statistics for year 2008 is:

Collaborating Hospitals	New cases	Follow up cases	Diagnosis coding	Treatment coding
(KFSH&RC, PSSC, Dammam Maternity & Children Hospital)	2337	4983	2247	12592

- 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.
- Data Request furnished for Proposal # 2081059, Congenital Cardiovascular Defects in Preterm Birth.
- Presentation on "Modeling Familial Co-Aggregation of Congenital Heart Defects: An Explanatory Data Analysis: from the CHD registry.

FUTURE DIRECTIONS

Collaborations.

PUBLICATIONS

- ↔ Multi-Institutional Cumulative Report (1998 – 2008).
- ↔ Maternal obesity and neonatal congenital cardiovascular defects Hala S. Khalil, MSc, Ahmed M. Saleh, MD, and Shazia N. Subhani, MSc. Int J Gynaecol Obstet. 2008 Sep;102(3):232-6.

Research Project: 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, and 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 ongoing from KFSH&RC and the collaborating hospitals; Disable Children Hospital, Maternity & Children Hospital, Dammam and Riyadh Medical Complex, Riyadh.

PROGRESS

- Data audited prior to annual report data tabulation.
- Agreement of collaborations and user trainings completed successfully for Maternity Children Hospital- Dammam, King Faisal Specialist Hospital- Jeddah, Al Qunfida Hospital - Medina and King Fahad University Hospital- Al-Khobar.
- On-going collaboration with Disable Children Association and Riyadh Medical Centre (RMC) Riyadh.
- Approval from MCO to utilize the hospital's outreach program for the expansion of the registry. Statistics for all year as of December 31, 2008 is:

	New cases	Diagnosis	Surgery
Collaborating Hospitals	3141	2420	362

- Statistics for year 2008 is:

	New cases	Diagnosis	Surgery
Collaborating Hospitals	521	775	173

- 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, King Fahad Medical City- Riyadh.

PUBLICATIONS

- Epilepsy Registry Cumulative Report (2008).

Research Project: 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, and Ms. Ebthisam Al Jarba

PROJECT DESCRIPTION

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

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.
- Several national presentations on registry data as follows:
 - ∞ “Team Approach in Cleft Care “Dammam Central Hospital, Dammam. Health Outreach Hospital Program KFSHRC.
 - ∞ “National Cleft Lip and Palate/Craniofacial Registry” 7th Arabic Congress of Pediatric Dentistry, Amman, Jordan.
 - ∞ Pediatric Grand Round “Dental Caries in Pediatric Population” Pediatric Department, KFSHRRC, Riyadh.
 - ∞ Dentistry Grand Round “Cleft Care in Saudi Arabia” Dental Department, KFSHRC, Riyadh.
 - ∞ “Team Approach in cleft Management”, King Fahad Medical City, Riyadh.
- Statistics for all year as of December 31, 2008 is:

	New cases	Diagnosis Coding	Treatment Coding
KFSH&RC	1088	1220	3577

Statistics for year 2008 is:

	New cases	Diagnosis Coding	Treatment Coding
KFSH&RC	109	337	280

FUTURE DIRECTIONS

Collaborations.

PUBLICATIONS

- ∞ Cleft Lip/Palate and Craniofacial Anomalies Registry Annual Report (2007).
- ∞ Pattern of Cleft Lip and Palate in Hospital-Based Population in Saudi Arabia: Retrospective Study. Aziza Aljohar, B.D.S., M.S., F.A.B.P.D., Kandasamy Ravichandran, Ph.D., Shazia Subhani, M.Sc. *Cleft Palate Craniofac J.* 2008 Nov;45(6):592-6. Epub 2008 Jan 29.

Research Project: 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 Naggar, Dr. Mona. El Sherif, Ms. Shazia Naz Subhani, and 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.
- Two presentations on registry data and software functionalities.
- Statistics for all year as of December 31, 2008 is:

	New cases	Follow up cases
K F S H & R C	2669	17421

- Statistics for year 2008 is:

	New cases	Follow up cases
K F S H & R C	283	2124

PUBLICATIONS

- ↳ Thromboembolic Disorders Registry Cumulative Report (2001 - 2007).

Research Project: Venous Thrombosis and Thrombophilia Disorders Registry (VTFT) RAC#: 2001 017.

Investigators: Dr. Jalal Saour, Dr. Layla Mammo, Dr. Mohamad Shoukri, Ms. Shazia Naz Subhani, Ms. Ehsan El-Shamy

PROJECT DESCRIPTION

The incidence and prevalence of venous thrombosis (VT) and venous thromboembolism (VTE) and their trend in Saudi Arabia is not known. However, there is a good reason to suspect that they will increase as the population ages, patients undergo and survive more major surgery, survive myocardial infarction, CVA and chemotherapy for malignancies. Thrombosis and Familial Thrombophilia Registry was initially initiated by the Coagulation Research Unit at the Department of Biological and Medical Research (now closed), Research Centre KFSH&RC in collaboration with the Registries Core Facility in Biostatistics, Epidemiology and Scientific Computing Department and Thromboembolic Service, Department of Medicine at the King Faisal Specialist Hospital and Research Centre, Riyadh. Now that the Coagulation Research Unit laboratory is non-functional, further genetic testing has stopped. However, we did get most of the information we set out to do i.e. which genetic factors are at risk for VT in Saudi population. We have recently got RAC approval to change the data acquisition forms with view of developing the current registry project as a national open registry with a proposed name Saudi Thrombosis and Familial Thrombophilia Registry (S-TAFT).

PROGRESS

- Case Report Forms re-designing for the national program.
- Clinic coverage for data acquisition and reporting.
- Presentations on registry data and software functionalities at Thrombosis & Hemostasis

Update Conference.

- Data presented in Pulmonary Symposiums – Marriot Hotel, Riyadh.
- Data presented in the Department of Medicine – Grand Round, KFSH&RC.
- Two podium presentations in the 20th international congress on Thrombosis Athens June 25-29, 2008.
- As of December 31, 2008 counts in the database is: 1085 cases.

FUTURE DIRECTIONS

National collaborations.

Research Project: 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, 2008 is:

	New cases	Diagnosis Coding	Treatment Cases
KFSH&RC	1682	1316	2211

- Statistics for year 2008 is:

	New cases	Diagnosis Coding	Treatment Cases
KFSH&RC	367	374	400

- Presentation on registry data: Neuromuscular Disorders in Childhood

PUBLICATIONS

- ↪ Neuromuscular Disease Registry 2007 Annual Report.

Research Project: National Diabetes Registry (Research Centre administration approved).

Investigators: Dr.Khalid Rubean, Dr. Mohamad Shoukri, Ms. Shazia Naz Subhani

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 2008, three more hospitals joined the registry. Currently there are 26 participating hospitals registering patients using the web-based on-line software.
- A "Best Paper Award" won at "Health GIS" International conference in Bangkok, Thailand.
- As of December 31, 2008 over 52,654 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"

FUTURE DIRECTIONS

Collaborations expansion on National Level.

PUBLICATIONS

- ↪ Various spin off research papers and abstracts.

Research Project: National Family Safety Registry (NFSR), RAC#: 2081 050.

Investigators: Dr.Huda Kattan, Dr. Maha Muneef, Majid Al Eissa, and Ms. Shazia Naz Subhani

PROJECT DESCRIPTION

The NFSP was initiated in November 2005 pursuant to the Royal Decree No. 11471/ MB with a mission to prevent child abuse and domestic violence in the Kingdom. The program is a collaborative project between different government and non-governmental agencies including the Ministry of Health and other

health service providers in the Kingdom that addresses the issue of child abuse and domestic violence.

With the increased number of reported case of child abuse, there is a rising need to initiate a national registry of child abuse. Collaboration between NFSP and King Faisal Specialist Hospital & Research Centre is mandated to develop a "state-of-the-art" registry.

PROGRESS

- Several meetings between the hospital's representatives.
- Agreement of understanding signed.
- Approval of the project proposal for registry design and development from Office of Research Affairs (ORA).
- Purchase and setup of the centralized web-server.
- Phase I design of the registry software.

Research Project: PanArab Liver Transplantation Registry (PALTS).

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

In March 2006, the 1st Pan Arab Liver Transplantation Congress was held in Cairo with great success. The meeting witnessed the birth of the Pan Arab Liver Transplantation Society (PALTS). One of the main goals of the Pan Arab Liver Transplantation Society was establishing a Web-Based Pan Arab Liver Transplantation Registry that will help in promoting and encouraging education, research and cooperation in the field of liver transplantation between various liver transplant programs in the Arab World.

Keeping in view this goal, in the year 2005 the first of its kind Pan Arab Liver Transplantation web-based registry was designed and developed and became prospective for the King Faisal Specialist Hospital as a part of Phase I of the registry objectives. This registry is a collaborative work between the Department of LTx and

Hepatobiliary-Pancreatic Surgery and, the Department of Biostatistics, Epidemiology and Scientific Computing (BESC).

PROGRESS

- Registry software presentations in Jordan March 2008.
- Establishment of new collaboration with Cairo University, Egypt.
- On-going collaboration with Wade-e-Nyle, Egypt.
- As of December 31, 2008 a total of 508 patients registered in the centralized database.
- On-going data collection and entry in the registry database.
- Submission of the First Annual Registry report.

FUTURE DIRECTIONS

Pan Arab Level Collaborations.

PUBLICATIONS

- ↪ First Annual Report 2008 on Pan Arab Liver Transplantation Registry data.

Research Project: 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

Project has been completed in year 2008.

PUBLICATION

- ↪ A scientific paper has been published (Maternal obesity and neonatal congenital cardiovascular defects Hala S. Khalil, MSc, Ahmed M. Saleh, MD, and Shazia N. Subhani, MSc. *Int J Gynaecol Obstet.* 2008 Sep;102(3):232-6.

Research Project: Congenital Cardiovascular Defects in Preterm Birth, RAC # 208 1059.

Investigators: Hala S. Khalil, MSc, Al-Halees Z, MD, Ahmed M. Saleh, MD, and Shazia N. Subhani, MSc

PROJECT DESCRIPTION

The objective of this project is to determine the prevalence of prematurity among infants with cardiovascular malformations. Also, to compare types and severity of congenital heart defects in preterm infants (< 37 completed week gestation) and term infants (> 37 weeks gestation). A retrospective case control study will be conducted

In this retrospective study we will review the congenital heart defect registry data for all newborn infants and up to the age of one year with isolated congenital cardiovascular defect(s) who had a preterm delivery between 1998-2006.

PROGRESS

Data is in the process of being extracted from patients' medical charts.

Technical Databases Core Facility

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

Head of Unit:

Saleh Al Ageel

Members:

Bushra Siddiqui

May Al Hussein

Lina Al-Fantoukh

Fahad Al-Enazy

Nirmal Sahar

APPLICATIONS (DEVELOPED AND BEING DEVELOPED IN THE YEAR 2008)

ORA ELECTRONIC SUBMISSION AND WORKFLOW SYSTEM

Office of Research Affairs (ORA) is a web-based application designed and developed to automate the processes required in research projects from submitting the proposal until producing the publication. Thus, different views and interfaces have been designed in order to facilitate these processes. It includes five interfaces.

- Investigator interfaces.
- Chairman interfaces.
- ORA interfaces.
- Pharmacist interfaces.
- Head of pharmacy interfaces.

The workflow starts when the investigator submits the proposal. This is done through filling electronic forms associated to selected study. After completing these electronic forms, the investigator has to submit it to the department chairman for approval. Once the proposal has been approved from the department chairman; the investigator has to submit it to ORA in order to review it along with the electronic forms. When ORA approve the proposal, RAC number will be generated and the investigator will be notified in order to start working on the project's report in the specified duration. After that, the investigator can submit the publication to ORA.

ORA interface is helping in automating the ORA daily work. Therefore, this application provides different electronic forms needed to be filled by ORA such as Budget, Sponsor Agreement, Animal Requests, Compliance Survey and archiving information. In addition, ORA user has to fill the main form which involves generating unique RAC number for each project. Additional task has been added to ORA user which is approving or rejecting any newly created users. This is practical solution to prevent anonymous users from accessing the application.

Security has been taken in consideration and there are different Security Mechanisms and techniques have been applied to achieve the highest level of security such as User Authentication, User levels, Sessions Timeout, Password encryption, locking users after few attempts to access the application and Confidentiality.

STEM CELL DEPARTMENT APPLICATION

A web-base application developed for The Stem Cell Therapy program department (SCTP). The application facilitates to save time and effort spent in reading and searching for electronic documents written by the staff. It also preserves the privacy of work and keeps the admin staff updated anytime anywhere about their staff's work.

The application's features

- PI , Co-investigator and technician will write his experiment online
- The experiment will be protected from unauthorized staff
- The experiment will be classified to its project
- The PI will see all experiments for all department unit projects
- The Co-investigator will see all experiments of his unit projects only
- The Technician will see only his experiments
- The experiments can be shared under defined SCTP rules
- The experiment will consist of the staff's work and will not be edited or deleted
- Guest user will see only public pages and cannot see the experiments

NATIONAL FAMILY SAFETY REGISTRY (PHASE I)

National Family Safety Registry (NFSR) is a cooperative work between the Research Centre and The National Family Safety Program .A web-based application designed and developed to provide electronic

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

MEDICAL SECOND OPINION APPLICATION

The Medical Second Opinion is a web-based application designed for the Health Outreach Office in King Faisal Specialist Hospital and Research Centre. The purpose of the application is to ease the work flow of requests that the office receives and provide the office with some statistics about the requests.

The application will enable the users to enter and update request information for medical second opinions electronically. The application has a flow of request feature from the requesting physician to the executive director. It will also provide the Health Outreach Office with a search feature and a reporting system for requesters, specialties requested, and service providers.

APPLICATIONS RE-DEVELOPED (NEW VERSIONS)

As the TDBCF 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 TDBCF using ASP Technology.

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

EPILEPSY REGISTRY

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

CLEFT LIP CLEFT PALATE & CRANIOFACIAL DISORDERS REGISTRY

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

APPLICATIONS (MODIFIED DURING YEAR 2008)

CONGENITAL HEART DEFECTS REGISTRY

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

THERMO LUMINESCENT 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 THROMBOPHELIA REGISTRY

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

MIDDLE EAST CHILDHOOD CANCER ALLIANCE (MECCA)

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

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 (VTFTR) 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 & MAINTAINANCE)

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.

SAUDI DIAGNOSTIC LAB (SDL)

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

CV'S DATABASE

Cv's database is a web-based application developed for RC Admin to keep all applicant CV's available electronically.

NEUROPSYCHOLOGY DATABASE

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

INSPECTION DATABASE

The hospital operations and project buildings department is in need of a system to keep track of the hospital buildings structure and inspections made throughout the year in order to present them to the JCIA visitors. Currently they are using excel sheets and papers to manage their work.

The TDBCF developed a web-based application that meets their requirements. The features of the software include adding/editing/deleting different kinds of buildings (main building, buildings, sub building...), adding/editing/deleting building's levels, adding/editing/deleting level's zones and adding/editing/deleting zone's rooms. In addition, the system allows the user to create/update zone inspections. Every inspected room can have up to four disciplines (arch, elect, mech, safety). A checklist questions must be filled for each discipline that includes the number of work requests generated for the discipline. The system can generate different types of reports as well.

NATIONAL PREMARITAL SCREENING APPLICATION

The National Premarital Screening Application is a cooperative work between the Research Centre and The Ministry of Health 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.

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.

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 CENTRE INVENTORY MANAGEMENT SYSTEM

The Research Centre 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

THE
BIOMOLECULAR
RESEARCH PROGRAM

The BioMolecular Research Program

The ultimate goal of the research program is to focus on discovery and target validation of molecular pathways that are perturbed as results of diseases which can be targeted by therapeutics. The research program employs the fields of functional genomics, functional proteomics and molecular therapeutics. To achieve this purpose, we narrow the human transcriptome and proteome to early and transient response players. Thus, the program is focused on important decision-making players in innate immunity, cell growth control and inflammation response including interferons, cytokines and negative feedback regulators. Specifically, the laboratory studies are aimed at the molecular pathways regulating mRNA stability in health and diseases and apply this knowledge for therapeutic purposes.

The recent focus on post-transcriptional regulation including its adaptability to high-throughput application will facilitate most of the program's objectives in the next few years. By using these 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.

Director:

Khalid S. Abu Khabar, PhD

Members:

Edward Hitti, PhD

Anas Al-Halees, PhD

Walid Moghrabi, MSc

Latifa Al-Haj, BSc

Maha Al-Ghamdi, MSc

Wijdan, Al-Ahmadi, BSc

Maher Al-Saif, BSc

Lina Omar

Suhad Al-Yahya

RESEARCH LINES AND PROJECTS

POST-TRANSCRIPTIONAL REGULATION OF GENE EXPRESSION

Studies required post-transcriptional assessment relying on the use of transcriptional inhibitors that have limitations or minimal promoters which have deficient expression levels. In this project, we developed transcriptionally non-inducible and constitutively active expression system suitable for selective post-transcriptional assessment. This approach will facilitate a number of research projects in the next few years including drug discovery program aimed at the utilization of post-transcriptional regulation platform.

CLONING-FREE TRANSCRIPTIONAL AND POST-TRANSCRIPTIONAL METHODOLOGY

The majority of the promoters, their regulatory elements and their variations in the human genome remain unknown. Reporter gene technology for transcriptional activity is a widely-used tool for the study of promoter structure, gene regulation and signaling pathways. Construction of transcriptional reporter vectors includes use of cis-acting sequences which require cloning and time-demanding manipulations particularly with introduced mutations. In this project, we developed a cloning-free strategy to generate transcriptionally-controllable linear reporter constructs as they are being applied in a number of inflammatory and innate immunity models.

ROLE OF RNA BINDING PROTEINS IN CELLULAR MRNA REGULATION

The aim of this project is to study large-scale functional properties of ARE-genes as influenced by RNA binding proteins and their relationship to inflammation and cancer.

COMPUTATIONAL BIOLOGY AND BIOINFORMATICS OF MRNA DESTABILIZATION ELEMENTS

Several studies are aimed to further explore the genome (human, mouse, and rat) distribution of AU-rich and GU-rich elements including various regions of the genes (5'UTR, CDS, and 3'UTR). Additionally, collaborative work on ARE-drosophila has been mostly concluded in this period.

OTHERS:

Various international collaborative research projects on modulation of gene expression by RNA binding proteins.

FUTURE RESEARCH DIRECTION

The program still shares the same focus and direction in the future. A large-scale view and analysis of RNA-stability changes during innate immunity and cellular growth will be facilitated by various tools that were developed in the past few years. Large-scale functional analysis of ARE-mRNA stability and post-transcriptional regulation in several cellular models of diseases will be performed.

PUBLICATIONS

- ✦ Wijdan Al-Ahmadi, Maha Al-Ghamdi1, Latifa Al-Haj1, Maher Al-Saif, and Khalid S. A. Khabar. Alternative Polyadenylation Variants of the RNA Binding Protein, HuR: Abundance, Role of AU-rich Elements, and Auto-Regulation. *Nucleic Acids Research*. In press.
- ✦ Nguyen Chi M, Chalmel F, Agius E, Vanzo N, Khabar KS, Jégou B, Morello D. Temporary regulated traffic of HuR and its associated ARE-containing mRNAs from the chromatoid body to polysomes during mouse spermatogenesis. *PLoS ONE*. 2009;4(3): e4900.

-
- ↪ Cairrao F, Halees AS, Khabar KS, Morello D, Vanzo N. AU-rich elements regulate Drosophila gene expression. *Mol Cell Biol*. 2009 Mar 9. [Epub ahead of print].
 - ↪ Al-Haj L, Al-Ahmadi W, Al-Saif M, Demirkaya O, Khabar KS. Cloning-free regulated monitoring of reporter and gene expression. *BMC Mol Biol*. 2009 Mar 8;10:20.
 - ↪ Al-Ahmadi W, Al-Haj L, Al-Mohanna FA, Silverman RH, Khabar KS. RNase L down modulation of the RNA-binding protein, HuR, and cellular growth. *Oncogene*. 2009 Mar 2. [Epub ahead of print].
 - ↪ Kanies CL, Smith JJ, Kis C, Schmidt C, Levy S, Khabar KS, Morrow J, Deane N, Dixon DA, Beauchamp RD. Oncogenic Ras and transforming growth factor-beta synergistically regulate AU-rich element-containing mRNAs during epithelial to mesenchymal transition. *Mol Cancer Res*. 2008 Jul;6(7):1124-36.
 - ↪ Papucci L, Witort E, Bevilacqua AM, Donnini M, Lulli M, Borchini E, Khabar KS, Tempestini A, Lapucci A, Schiavone N, Nicolini A, Capaccioli S. Impact of targeting the adenine- and uracil-rich element of bcl-2 mRNA with oligoribonucleotides on apoptosis, cell cycle, and neuronal differentiation in SHSY-5Y cells. *Mol Pharmacol*. 2008 Feb;73(2):498-508. Epub 2007 Nov 7.
 - ↪ 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.
- INVITED TALKS AND ORAL PRESENTATIONS**
- Invited Keynote Speech: Cell-Based Assays: Sensing the Possibilities: Cell-Based Assays Conference. London, November 2008.
 - Invited Plenary Session Speech: 2008. Khabar, K.S. Bioinformatics and Experimental Systems for Post-transcriptional Assessment of Gene Expression. RNA turnover 2008. October 12-16, Ashville, NC, U.S.
 - Research Centre Seminar: Ribonuclease L regulation in innate immunity and cellular growth. March 2008.
 - Khabar, K.S. 2008 Molecular response to therapeutic interferons: Sensitivity and resistance mechanisms. 1st International Conference on Drug Design & Discovery. Dubai. February 4-7.
 - Invited Keynote Speech: Khabar, K.S. 2007. Gene regulation in innate immunity and cellular growth: The Rapid Transit. Science Horizons Conference, Riyadh.

PATENT APPLICATIONS

1. Method of generating translationally active linear DNA molecules and use thereof in array formats (EP, CA, US, 2007).
2. Hybrid 3'-untranslated regions suitable for efficient protein expression in mammalian cell (EP, CA, US, 2008).
3. International Patent Application. June 27, 2008. PCT/EP2008/005278. "Cloning-Free Method of Generating Transcriptionally and Post-Transcriptionally Controllable Expression Active Linear Reporter Constructs".
4. International Patent Application. November 17, 2008. PCT/EP2008/009712. "Expression Vectors Based on Modified Ribosomal Protein Promoters and Uses Thereof in Post-Transcriptional Assessment".

THE 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. The Bioanalytical Laboratory of the CCSEE has been accredited by the College of American Pathologists (CAP) since May 2007. The gross income for the year 2008 was SR 290,000.00. For the last few years, the CCSEE has been expanding in the empirical ethics field.

PROJECT / STUDIES

DRUG ASSAY DEVELOPMENT AND VALIDATION

No.	Drug Name	Analysis Method	Volume (ml)	Matrix	Range (µg/ml)	Date Completed
1.	Gemfibrozil	HPLC-FL	0.1	Plasma	0.1-100	July 2008
2.	Hydrochlorothiazide	HPLC-UV	1.0	Plasma	0.005-0.3	Nov 2008
3.	Itraconazole	HPLC-FL	1.0	Plasma	0.02-5	May 2008
4.	Losartan	HPLC-UV	0.5	Plasma	0.02-9	June 2008
5.	Ibuprofen 1	HPLC-FL	0.1	Plasma	0.1-8	July 2008
6.	Ibuprofen 2	HPLC-FL	0.1	Plasma	5-100	Nov 2008
7.	Doxycycline	HPLC-UV	0.1	Plasma	0.1-10	Nov 2008
8.	Meloxicam	HPLC-UV	0.5	Plasma	0.05-2	Oct 2008
9.	Cetirizine	HPLC-UV	0.5	Plasma	0.04-2	Dec 2008

Director:

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

Co-Director:

Maha Al Saud, MD

Members:

Abdelraheem Ahmed
Ahmed Yusuf, BSChem
Eman Al-Gaai, RPh, CCRP, MHHA
Fawaz Abdullah Alturki, MD
Hunida Abdulhameed, RPh
Ma. Lourdes Bautista
Ma. Victoria G. Ventura
Mohammed Alsunaid, MD
Mohammad Al-Qadire, SN
Nada Bin Hashim, RN
Rajaa Hussein, RPh
Reem Al-Swayeh, RPh
Sahar Atalla, MBBCh, MS
Saleh Al-Dgither
Syed N. Alvi, PhD
Weam Al-Jasim, RPh
Yousef Al-Jawarneh, RN

CLINICAL

Project Title: Measuring Placebo Effect by Elimination and Investigating Its Mechanism of Action, RAC#2051 072 (Funded by KACST: Project # AT-26-45).

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.

PROGRESS / MAJOR FINDINGS

Preparing manuscript.

Project Title: How Much Do Outpatients Know About Their Medications? RAC# 2071 077.

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.

PROGRESS / MAJOR FINDINGS

Recruiting.

Project Title: Salivary Testosterone Level in Healthy Male Arabs, RAC# 2071 081.

PROJECT DESCRIPTION

Accurate determination of biologically-available testosterone levels is fundamental to studying physiological and pathophysiological androgenic status. Measuring salivary testosterone level is convenient, non-invasive, and accurate. We plan to develop and locally validate a liquid chromatography mass spectrometry 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.

PROGRESS/MAJOR FINDINGS

Developing assay.

Project Title: Sodium Bicarbonate in Preventing Contrast Induced Nephropathy (SIPCIN): A randomized controlled study, RAC # 2071 003.

PROJECT DESCRIPTION

Contrast-induced-nephropathy (CIN) is not an uncommon disease that is associated with important morbidity and mortality, particularly in high risk patients. The strategy of choice to prevent CIN has not been established. Traditionally, intravenous or 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 6 hours after procedure) has recently been shown to be associated with impressive results; however, it has not 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 be stratified according to the presence or absence of DM, or an estimated GFR 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 0.5 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.

PROGRESS / MAJOR FINDINGS

Recruiting.

Project Title: Public View and Saudi Preferences: Patient Desire for Medical Information, and Participation in Clinical Decision Making, RAC#2081 058.

PROJECT DESCRIPTION

A physician, from moral and ethical responsibilities is required to involve patients in clinical decision making,

providing full information about the patient's health situation. Not every patient may want the same level of information and participation in clinical decision making. The medical decision is very much controlled by a family member in countries such as in Saudi Arabia. Furthermore, many other factors may influence the patient preference regarding the issue. We are planning to conduct a study in a population-based survey of a representative sample of 1000 adult Saudi patients and their companion attending KFSH&RC, Riyadh, to assess public preferences for patient desire for information, and participation in clinical decision making, family involvement in the decision and to assess other demographic variables, as gender differences, female patients compared to male in the decision context, and desire for information. The results are expected to help health care professionals to provide the patients with the type and amount of information that meet their needs, also may lead to increase patients satisfaction with medical decisions, and consequently to better compliance and better outcomes.

PROGRESS / MAJOR FINDINGS

Recruiting.

Project Title: Association of PROP Taster Status With Food Preferences and Its Effect on Body Mass Index, RAC# 2081 115.

PROJECT DESCRIPTION

Individuals' variation in taste perception of phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP) was first noticed in 1930s. However, the association between PTC sensitivity and food preferences did not begin to develop until the 1960s. Whether there is a link between PROP taster status and food preferences, and hence obesity, or not is not clear yet; such influence is still a matter of debate. In this proposal, we aim to determine the influence of PROP taster status on food choices and whether this has any effect on weight. Subjects will be classified as supertasters, medium tasters, or nontasters using suprathreshold rating procedure. The effect of PROP taster status on food

choices will be measured by rating the likeness of bitter food using self-reported checklist for 15 foods. Weight and Body Mass Index will be used to assess the effect of PROP taster status on weight status. The results of this study are expected to provide a better understanding of factors that influence food selection. Such understanding may encourage health practitioners to work on better strategies for dietary change.

PROGRESS / MAJOR FINDINGS

Under review by RAC.

EMPIRICAL ETHICS

Project Title: Medical Chaperoning at KFSH&RC: Physicians' Views, RAC#2071 011.

RESULTS SUMMARY

Aim: To examine physicians' use and perception of MC in Islamic culture. **Setting:** A major tertiary care hospital in Saudi Arabia. **Methods:** 315 self-administered questionnaires with a cover letter were distributed to attendees of grand rounds of 13 departments. **Participants:** Attendees of grand rounds. **Results:** 186 (59%) questionnaires were completed. 64.5% of the respondents were 30-49 years old, 75.8% males, and 31.2% in-training; 79% had a clinic load of < 50 patients per week, and 47.8% had postgraduate training (PGT) in an Islamic country. MC was reported to be infrequently ($\leq 25\%$ of the time) used by 44.1% (69.2% female versus 39% male physicians, $P=0.001$; 58.6% in-training versus 36.8% attending, $P=0.007$; 52.1% PGT in Islamic versus 35.6% in Western countries, $P=0.027$), offered by 52.7% (78.9% female versus 46.8% male physicians, $P< 0.001$), and requested by 79% patients. MC was reported to be commonly ($>75\%$ of the time) used, offered by physicians, and requested by patients by 38.2%, 29%, and 7.5%, of the respondents respectively. 49% of the 104 frequent MC users ($> 25\%$ of the time) did not report using a staff nurse as the most frequent MC. The most frequently cited reasons for not using MC were privacy/confidentiality (36.6%) and understaffing (30.5%). Equal numbers of respondents perceived MC

use as a protection for physicians or patients (67.7% and 65.6%, respectively). **Conclusions:** MC is underutilized even in Islamic culture, especially among female physicians. Training in Western countries is favourably associated with MC use. The underutilization appears to be related to privacy/confidentiality, understaffing, and failure of patients to request an MC.

PROGRESS / MAJOR FINDINGS

Completed.

Project Title: Disclosure of Medical Errors: KFSH&RC's Patients and Physicians Attitudes, RAC#2071 054.

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.

PROGRESS / MAJOR FINDINGS

Enrollment is about 80% completed.

Project Title: Consenting Options for Organ Donation: A Survey of the Opinions and Preferences of Saudi, RAC#2071 068.

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 KFSH&RC 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.

PROGRESS / MAJOR FINDINGS

Enrollment is about 35% completed.

Project Title: Patients' Perception of Informed Consent: Function and Required Information, RAC#2081 002.

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.

PROGRESS / MAJOR FINDINGS

Recruiting.

Project Title: Prognosis Disclosure to Terminal Patients: Governing Codes in Islamic and Arabic Countries, RAC#2081 024.

RESULT SUMMARY

The disclosure of diagnosis/prognosis of terminal to illness patients and/or their families continues to be an area of controversy and health care workers are left perplexed. We reviewed parts of the available codes of medical ethics from Arabic and Islamic countries that addressed disclosure of terminal illness and compared them with international and prevailing western codes. The codes were classified independently by the authors into silent, allowing, mandating or prohibiting. The few discrepancies that arose were solved by discussion. Codes from 12 Arabic and 2 Islamic countries were located. 36% of the codes were silent regarding informing the patient, 36% allowed concealment, 21% mandated disclosure, and 7% suggested not to inform patients. In comparison, the code of the World Medical Association (WMA) allowed concealment, the Canadian code was silent, and the UK and US mandated disclosure. On the other hand, 25% of the codes were silent regarding informing the family, 33% allowed disclosure (if necessary or unless patient wishes otherwise), 47% mandated disclosure (across the board or when concealing from patient, or as appropriate), and 7% prohibited informing the family without patient permission. In comparison, The WMA code allowed disclosure to family after taking

patient consent. The Canadian, UK, US codes allowed disclosure to a patient designated proxy. Codes regarding disclosure of terminal illness to patients and families markedly differ among Arabic and Islamic countries. In comparison with international/western codes, they overall tend to favor a paternalistic/utilitarian approach rather than autonomy centered approach.

PROGRESS / MAJOR FINDINGS

Preparing manuscript.

Project Title: Written versus Verbal Information in Consenting for Thyroidectomy: Patient Satisfaction and Information Retention, RAC#2081 047.

PROJECT DESCRIPTION

A written informed consent is an ethical and legal requirement for surgical procedures. The information required for consenting can be provided in a verbal, unstructured format (traditional), or in a documented, structured format. The type of format may affect patients' satisfaction and the amount of information they retain. We plan to compare the two formats in regards to patient satisfaction and degree of information retention as well as perception of the role of consenting, time-cost, and practicality, in a randomized single-blinded study. Eligible patients requiring thyroidectomy will be block-randomized, to either format, at the time of scheduling for surgery. The structured format has been adopted from the literature. For the traditional format, the currently used generic form will be used, and the information to be verbally provided will be based on the recording of 3 traditional consenting episodes. Consenting using either format will be performed by one investigator. On the first post-operative outpatient visit, the participants will be informed about the study and asked to complete questionnaires on information retention, perception of the role of consenting, and patient's satisfaction, after obtaining their verbal consent. Preliminary questionnaires have been developed by the investigators and will be pre-tested on 5 thyroidectomy patients and 3 thyroid surgeons and modified accordingly.

The questionnaires will be administered by an investigator blinded to participant's assignment. The two formats will be compared using the unpaired, two-tailed t-test. A Chi square test will be used to compare responses to individual statements (for patient satisfaction questionnaire). The results of the study are expected to provide empirical evidence on the efficacy as well as time-cost of the structured format for thyroidectomy (and indirectly for similar surgeries) and help physicians and policy makers improve patients' care and satisfaction.

PROGRESS / MAJOR FINDINGS

Enrollment is 15% completed.

Project Title: Saudis End-of-Life Priorities: Patterns and Extent of Sharing With Family Members and Physicians, RAC#2081 057.

PROJECT DESCRIPTION

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

Saudi view(s) and contribute to global bioethics on EOL as well.

PROGRESS / MAJOR FINDINGS

Recruiting.

Project Title: Ethical Approval of Human Subjects Published in Saudi Medical Journals, RAC# 2051 030.

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. This study specifically aims to review the documentation of the compliance with ethical guidelines in studies on human subjects conducted in Saudi Arabia and published in Saudi Journals from January 1980 to December 2007.

PROGRESS / MAJOR FINDINGS

2,658 articles in 15 journals have been reviewed. Data collection is 70% completed.

Project Title: Modeling Ethical Resolution: Mapping Points of Ethical Equilibrium, RAC#2060 004.

PROJECT DESCRIPTION

Making decision on ethical issues is based on beliefs and on balancing several ethical values/principles. The different ways individuals of different backgrounds use and balance ethical principles have not been well defined. We propose to use Q methodology to identify models of ethical decision-making and points of ethical equilibrium in regards to three controversial bioethical topics including the acceptance of placebo use in medicine. Several Q-sets will be constructed and examined for reliability and validity. The extent people use ethical principles other than those described in the four-principles-plus-scope approach (i.e., respect for autonomy, beneficence, non-maleficence, and justice) will be examined. The association

of various demographic factors with the identified models and the effect of formal ethical education will be studied. We will also explore the stability of the identified models/points of equilibrium over time, within demographic groups, and across topics. The results are expected to have important contributions to empirical studies of ethical resolution and to evidence-based ethics regarding current bioethical issues. It may show that beliefs aside, ethical resolution models/points of equilibrium may not be different across nations or segments of society. It will also provide empirical evidence for or against the adequacy of the simplified four-principles-plus-scope approach in biomedicine.

PROGRESS / MAJOR FINDINGS

On-going.

Project Title: Public View on Consenting for Retrospective Research on Medical Records or Leftover, RAC #2071 031.

RESULT SUMMARY

Consenting for medical records-based research (MRR) and leftover tissue-based research (LTR) continues to be controversial. We surveyed 528 Saudis attending clinics at a tertiary care hospital in Saudi Arabia to explore their personal preference (PP) and perception of what is generally appropriate (GA) and currently practiced (CP) regarding consenting for MRR and LTR. The respondents selected one of 7 options for each of 6 questionnaires. Their mean (SD) age was 33 (11), 42% were males, 56% were patients, 85% had \geq secondary school education, and 9% volunteered previously for research. 39% and 49% considered it GA to conduct MRR and LTR, respectively, without consent, 23% and 30% without ethics committee review, and 23% and 21% not to allow such research. There was no significant difference in the distribution of choices according to age, gender (except for MRRPP, $P = 0.001$), health status (except for LTRCP, $P = 0.002$), or previous research participation, nor between PP and GA. However, there was significant difference related to educational level

in MRRPP ($P < 0.001$) and MRRGA ($P = 0.001$), between LTR and MRR (for GA and PP, $P = 0.002$), and between LTRCP and LTRGA ($P = 0.001$). We concluded that: 1) there is a considerable diversity among Saudis regarding consenting requirement for MRR and LTR, which is related to educational level but not age, gender, health status, or having volunteered in research. 2) Stricter requirements were expressed for MMR (vs. LTR) and for LTRGA (vs. LTRCP).

PROGRESS / MAJOR FINDINGS

Manuscript submitted.

Project Title: Verbal versus Written Anesthesia Consent: Patient Satisfaction and Information Retention, RAC#2081 112.

PROJECT DESCRIPTION

A written informed consent is an ethical and legal requirement for surgical procedures. Consent for anesthesia per se is usually obtained during the preanesthetic visit separate from the surgical consent. The information required for consenting can be provided in a verbal, unstructured format (traditional), or in a documented, structured format. The type of format may affect patients' satisfaction and the amount of information they retain. We plan to compare the two consenting formats in consenting for anesthesia in regards to patient satisfaction and degree of information retention as well as time-cost, in a randomized single-blinded study. Eligible patients requiring elective surgery will be block-randomized, to the structured or traditional format, at the time of the preanesthesia visit. The structured format has been adopted from the literature. For the traditional format, the currently used verbal method will be used, and the information to be verbally provided will be based on the recording of 3 traditional consenting episodes. Consenting using either format will be performed by one investigator. Before surgery, the participants will be consented for the study and asked to complete 2 questionnaires on information retention and patient satisfaction. Preliminary questionnaires have been developed by the investigators and will be pre-tested on 5

patients and 3 anesthetists and modified accordingly. The questionnaires will be administered by an investigator blinded to participant's assignment. The two formats will be compared using the unpaired, two-tailed t-test. A Chi square test will be used to compare responses to individual statements (for patient satisfaction questionnaire). The results of the study are expected to provide empirical evidence on the efficacy as well as time-cost of the structured format for anesthesia and help physicians and policy makers improve patients' care and satisfaction.

PROGRESS / MAJOR FINDINGS

Under review by RAC.

TRAINING AND EDUCATION

1. 7th Clinical Research Professionals' Course, 19 to 30 January 2008 (60.25 CME hours with commendation by the AACME and 30 CME credit hours by the Saudi Council).
2. 1st Semiannual LC&LCMS: Concept and Hands-On Training Course, 5 to 9 April 2008 (17 CME credit hours by the SCHS).
3. 8th Clinical Research Professionals' Course, 31 May – 11 June 2008 (62.25 CME hours with commendation by the AACME and 30 CME credit hours by the Saudi Council).
4. 9th Semiannual Clinical Research Professionals' Course, 8 to 19 November 2008 (64.75 CME credit hours with commendation by the AACME and 57 CME credit hours by SCHS).

PUBLICATIONS

- ↪ Syed N. Alvi, Saleh Al-Dgither, and Muhammad M. Hammami. Validated LC-MS/MS Assay For The Determination Of Ramipril Levels In Human Plasma. *Analytical Chemistry*. Vol.7, Issue 7, 2008.
- ↪ Syed N. Alvi, Muhammad M. Hammami. Simultaneous Determination of Sulfamethoxazole and Trimethoprim in Human Plasma by RP-HPLC. *Analytical Chemistry*. Vol.7, Issue 8, 2008.

THE DEPARTMENT OF
COMPARATIVE MEDICINE

The Department of Comparative Medicine

The mission of the Department of Comparative Medicine (DCM) is to develop and utilize various animal models in order to study the cause and nature of diseases and to assist the research activities of the Hospital & 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 Training and teaching programs in animal use for research and participating in experimental surgery courses with other departments (Neurosciences, General Surgery, Obstetric Gynecology, Urology).
- d. Provide accredited facilities for housing laboratory animals.
- e. Consult and collaborate with research personnel to assist in project planning and technique development.
- f. Institutional compliance with animal welfare regulations, standards and policies.

The DCM also conducts in-house research activities in areas pertinent to the Kingdom of Saudi Arabia such as heatstroke, tuberculosis and cardiovascular diseases.

Chairman:

Raafat M. EL-Sayed, DVM, MVSc

Administrative Support Staff:

Lorie Belarmino

Perlie F. Bohol

Ma. Cecilia Badajos

THE COMPARATIVE MEDICINE DEPARTMENT CONSISTS OF

RESEARCH UNITS

1. Heatstroke research and Cell Injury & Inflammation Research Unit
2. Tuberculosis Research Unit
3. Microbial Immunology

CORE FACILITY UNIT

1. Laboratory Animal Core Facility
2. Experimental Surgery

EXPERTISE

1. Development and/or provision of various animal models of important human diseases including transgenic mice.
2. Expertise in veterinary care for a large variety of laboratory animal species including rats, mice, rabbits, cats, guinea pigs, hamsters, sheep, dogs and baboons.
3. Expertise in conducting both clinical and basic research (heatstroke, sepsis, infectious diseases).
4. A well equipped surgical theatre for general laparoscopic, micro- and cardiovascular surgery for research and training
5. A microsurgery suite equipped with latest generation of microscopy

PUBLICATIONS

- ↔ Bouchama A, Kunzelmann C, Dehbi M, Kwaasi A, Eldali A, Zobairi F, Freyssinet JM, de Prost D, (2008). Recombinant activated protein C attenuates endothelial injury and inhibits procoagulant microparticles release in baboon heatstroke. *Arterioscler Thromb Vasc Biol.* #28:1318-25.
- ↔ Roberts G, Chishti M, Al-Mohanna F, El-Sayed R, Bouchama A. (2008). Microvascular injury, thrombosis, inflammation, and apoptosis in the pathogenesis

of heatstroke: a study in baboon model. *Arterioscler Thromb Vasc Biol.* #28: 1130-6.

PRESENTATION

Dehbi M. et al., (2008). Expression profiling of heat shock proteins in a primate non-human baboon model of heatstroke. The Cold Spring Harbor Lab. Meeting on Cell Stress & Chaperones. New York, USA (Apr. 29 to May 4. 2008).

ACADEMIC TRAINING AND WORKSHOPS

A number and variety of workshops and educational trainings offered by the Laboratory Animal Facility and Experimental Surgery of DCM in collaboration of various hospital departments.

WORKSHOPS

Activities	Number of Participants	Number of Animals Used
Microsurgery Course (2 workshops)	10	105 rats
Residents Vascular Surgery & Laparoscopic Workshop	20	3 dogs
Residents Anastomosis & Laparoscopic Workshop	36	3 dogs
Life Support Training Center	23	1 sheep
TOTAL	221	132

TRAINING AND EDUCATIONAL ACTIVITIES

Training Program	Animals Used	Training Period
Assisted Ms. Najla Al Abdulsalam, MS student from King Faisal University, Hofouf for her MSc Project: <i>Effect of Dexamethasone on Pregnancy Outcome & Development of the liver in SD Rats.</i>	SD Rats (250 Rats)	Completed 2008
Assisted Ms Mouna Al-Amoudi from Physiology Department, Girls College, Riyadh on her PhD Project: <i>A Correlation Study Between Low Protein Diet and The Renal Hypertensive Injury in rats.</i>	Hypertensive Rats	Ongoing
Provided basic surgery training to 3 undergraduate medical female students from college of medicine, KSU.	Small & large animal	August 2008 (1 month)
Provided one month summer training for 4-5 male high school students of Ibn Sena Program, King Abdulaziz and his Companion Foundation for the Gifted.	Mice/Rats	July 2008 (1 month)

COLLABORATIONS

The DCM has developed a large network of collaborators both locally and internationally.

NATIONAL COLLABORATIONS

- KFSHRC, Riyadh
- National Guard Hospital, Riyadh
- National Commission for Wildlife Conservation and Development, Taif
- King Saud University, College of Medicine, Pharmacy, Science and Girls College.
- King Faisal University, College of Veterinary Medicine.

- Ibn Sena Program, King Abdulaziz and his Companion Foundation for the Gifted.

INTERNATIONAL COLLABORATIONS

- United States of America: Eli-Lilly & Company, Indianapolis
- Canada: University of Toronto, Toronto
- Netherlands: National Institute of Public Health & Environment
- World Health Organization: European Centre for Environment and Health
- France:
 - ↔ INSERM, Paris
 - ↔ Hopital Louis Mourrier, Paris
 - ↔ Universite Louis Pasteur, Strasbourg
 - ↔ Institut Pasteur de Lille, Lille
 - ↔ Institut Pasteur de Guadeloupe, Guadeloupe
- United Kingdom: Royal Free University, London

OTHER ACHIEVEMENTS

Construction of a new DCM.

FUTURE GOALS

- Prepare for the accreditation by the American Association for the Accreditation of Laboratory Animal Care International.
- To Establish small animal imaging Facility.
- To Establish a veterinary diagnostic lab: for genetic and health monitoring.
- To Establish Animal Physiology and Pharmacology Lab.
- To Establish Antibody Production Facility.
- Establish Reproductive Biology and Transgenic Core Facility.
- Strengthen the collaborations and links.
- Focus on translational research by conduct more pre-clinical trials on relevant species in collaboration with various departments within and outside KFSH&RC.

Experimental Surgery, Animal Facility Research Unit

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.

Head of Unit:

Ra'afat M. El-Sayed, DVM, MVSc

Members:

Falah H. Al-Mohanna, DVM

Mohammed Hassan, DVM

Ludivina A. Apilado

Sahar I. Salem

Merfat A. Elyan

Saad Al-Durgham

SERVICE WORK

The Experimental surgery suite is fully equipped with state of the art surgical equipments to ensure the success of all surgical procedures. These equipments are anaesthesia machines and monitoring equipments heart-lung machine, defibrillator, diathermia, Pulse-oximeter, echocardiogram, urodynamic machine. Fluoroscopy, Laparoscopy and Endoscopy equipments and facilities are also available. Blood gas machine, haematology analyzer and other relevant instruments are in place. Expertise is also available to support routine, research and specialized surgical procedures.

- Provide support and services for experimental surgery requirements of various research.
- 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.
- Well-equipped surgical theatres, facility and staff are available to provide major surgical research obligations in cardiovascular, general, dental, laparoscopic, transplantation, microsurgery, neuroscience and urological surgery subspecialties.

TRAINING & WORKSHOPS

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:

- Microsurgery
- Laparoscopy
- Endoscopy
- Bowel Anastomosis
- Vascular Surgery

- General Surgical procedures
- Difficult Airway Management
- Life Support Training

OBJECTIVES

- To promote & improve surgical practice and skills
- To enhance the knowledge of new skills and techniques in minimally invasive surgery
- 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:

- An operating table
- Instrument table with all necessary surgical instruments
- Monitoring Vital Signs Equipment (ECG, Heart Rate, RR, Invasive and non invasive blood pressures and Oxygen Saturation)
- Anaesthesia machine
- IV Pump and Syringe Pump

LAPAROSCOPY & ENDOSCOPE TOWER

- Endoscope camera coupled with a cold light source
- TV monitor
- Insufflator
- Vacuum suction irrigation system

TRAINING IN MICROSURGERY (MICROSURGERY ANIMAL LAB)

The Microsurgery Animal Laboratory at CMD of the Research Centre in collaboration with the KFSH Departments offers two types of training courses:

- Continuous weekly training courses held 4-5 times per week morning and afternoon for hospital staff and candidates from other institutes & hospitals in the Riyadh area.
- The Intensive courses are given 4-6 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.
 - ∞ Training programs:
 - To include the following exercises
 - Operating microscope: basic principles of microsurgical instruments and suture material
 - Preparation for microsurgery:
 - Body posture
 - Hand position
 - Handling Microsurgical sutures and needles:
 - Warm-Up Exercise
 - Hand and wrist movements under microscope.
 - ∞ Flexing and extending the wrist, rolling the needle holder and tying forceps between thumb and index finger.
 - ∞ Glove-Rubber Practice card:
 - Initial suture exercise on a piece of glove rubber stretched out on a practice card.
 - Knot-Tying Exercises
 - Correct knot tension
 - Cutting suture
 - ∞ Rat Aorta
 - Rat Anaesthesia and preparation
 - Rat Anatomy and dissection
 - Vascular Exercises in rat
 - Practice End-to-end anastomosis
 - Practice End-to-side anastomosis.
 - ∞ Thymectomies & Vasectomies in rodents

Microsurgery Animal Lab is equipped with 6 microscopes with video camera and LCD TV.

The following departments use the Microsurgery Animal Laboratory:

- Department of Neurosurgery
- Department of Urology
- Liver Transplantation
- Orthopaedic
- Department of Plastic Surgery
- 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:

- Intra-abdominal orientation is carried out from diaphragm to the pelvis, learning tactile and feedback and depth perception.
- Once the candidate is comfortable with that aspect of training (orientation), they will proceed with some actual procedures, which will involve:
 - ∞ Appendectomy; removal of appendix
 - ∞ Cholecystectomy; removal of gall bladder
 - ∞ Splenectomy; removal of spleen
 - ∞ Nissen fundoplication
 - ∞ Gynaecology: Tubal Ligation, Ovarian Cystectomy, Oophorectomy, Vaginal Hysterectomy Pelvic Lymphadenctomy
 - ∞ 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 departments that use the Laparoscopy Animal Laboratory:

- Department of Gynaecology & Obstetric
- Department of Urology
- Department of Surgery
- Cardiovascular Department

The following attendants use the Laparoscopy Animal Laboratory:

- Minimally Invasive & Robotic Surgeons
- General & Specialist Surgeons
- Residents
- Doctors interested in minimally invasive surgery
- Other health care providers.

Training in Bowel Anastomosis, Vascular Surgery & General surgery procedures

- Vascular Surgery:
 - Dissection of Carotid Artery and Jugular vein
 - A.V. Fistula Creation
 - Closure of carotid defect
- Bowel surgery:
 - Gastrointestinal orientation and exploratory examination
 - Gastro Enterotomy
 - Gastrectomy
 - Roux En Y Reconstruction
 - Bowel Resection & Anastomosis

FACTS AND FIGURES

Workshops, Training and Education in Collaboration with Hospital Departments, Performed in Year 2008.

Training & Workshops	Details
Microsurgery, Intensive Course, each course 5 days per week	3 courses, 130 rats 13 participants 2 Instructors
Laparoscopy and Bowel Vascular Anastomosis for Residents, Two seasons	1 workshop, 3 dogs 6 participants 2 Instructors

Laparoscopy and Bowel Anastomosis & General Surgery procedures for Residents, Two seasons	1 workshop, 3 dogs 16 participants 6 Instructors 3 OR nurses
Life Support Training Fundamental of Critical Care Support	30-35 participants 2 sheep
TOTAL	Participants : 72 Instructors: 10 Dogs: 6 Sheep: 2 Rats: 130

WORKSHOPS

Training & Workshops / RAC #	Principal Investigator / Department	Date	# of Participants	Animals Used
Laparoscopy & Vascular Surgery Training and Suturing Techniques RAC # 2032 004	Drs. Bassel Safi Dept. of Surgery	24 April 2008	6 participants 3 instructors+ 2 OR nurses+ 7 LAF staff (in 2 sessions)	3 dogs
Bowel Anastomosis, general surgery procedures and Laparoscopy RAC # 2032 002	Drs. Alaa Abdul Jabbar & O' Regan / Dept. of Surgery & Tyco Healthcare	15 May 2008	14 participants 3 instructors 2 OR nurses+ 7 LAF staff (in 2 sessions)	3 dogs
Life Support Training Centre: Fundamental of Critical Care Support	Dr. Sulaiman Al Hosaini	22 July 2008	20 participants	1 sheep
Microsurgery Intensive Course RAC # 2022 008	Dr. Essam Al Shail / Dept. of Neurosciences	January 5-9 2008	4 participants 2 instructor	40 rats
Microsurgery Intensive Course RAC # 2022 008	Dr. Essam Al Shail / Dept. of Neurosciences	March 1-5 2008	4 participants 2 instructor	40 rats
Microsurgery Intensive Course RAC # 2022 008	Dr. Essam Al Shail / Dept. of Neurosciences	May 3-7 2008	5 participants 2 instructor	50 rats

MICROSURGERY WEEKLY TRAINING

Microsurgery RAC # 2022 007	Dr Ali Al Malaq, Plastic Surgery	Every Wednesday	5 participants 1 instructor	10 Rats
Microsurgery Training RAC# 2082 001	Dr. Raouf Seyam, Department of Urology	Every Sunday	1-2 participants	28 rats
Transpericardial Access Training RAC# 2082 002	Drs Fareed Khouqeer & Kandeel Cardiac Surgery	Occasionally	2 participants	5 rats
Microsurgery Training RAC# 2082 003	Dr. Moh'd Al-Sebayel Liver Transplantation Surgery	Occasionally Every Monday	5 participants	5 rats

TRAINING AND EDUCATIONAL ACTIVITIES

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)	Completed 2008
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	Ongoing
Provided basic surgery training to 3 undergraduate medical female students from college of medicine, KSU	Small & large animal	Aug 2008 (1 month)
Provided one month summer training for 4-5 male high school students of Ibn Sena Program, King Abdulaziz and his Companion Foundation for the Gifted	Mice/Rats	July 2008 (1 month)

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:

FUTURE PLAN

- Furthermore, work is in progress to establish Surgical Training Centre with additional laparoscopic surgical theatres Linked by an interactive multimedia teaching system, which displays different kinds of images, small animal surgical procedures, surgical laparoscopic procedures and endoscopic view.
- To establish a training centre in collaboration with the Departments of Surgery, Neuroscience Urology, and Cardiovascular Surgery at King Faisal Specialist Hospital and Research Centre.

Research Project / P.I. / Department	No. of Animals Used	RAC Approved No. of Animals
RAC# 2050 032. The Effect of a Adrenergic blockers on the ureter: an in vivo study in the dogs. Dr. R. Seyam. Dept. of Urology	19 dogs 2007	20 dogs
RAC# 2031 086. Optimization of tunica albuginea free graft for coporoplasty; an experimental Baboon animal study. Dr. R. Seyam. Dept. of Urology	14 baboons 2007	26 baboons
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 2007	10 dogs
RAC# 2030 088 Phase I&II. Myocardial Infarct Model in Baboons. Dr. C. Mullangi. King Faisal Heart Institute	10 baboon 17 cardiac surgery	10 baboons, used
RAC# 2030 088 Phase I&II. Myocardial Infarct Model in Baboons. Dr. C. Mullangi. King Faisal Heart Institut Follow up	5 cardiac procedures, inject of stem cells	6 baboons alive
RAC# 2080 018. Piolt Study on Penile Auto-Transplantation in Baboon: Function Outcome. Dr. R. Seyam. Dept. of Urology	1 baboon 2008	3 Baboons

Heatstroke & Cell Injury & Inflammation Research Unit

Excessive inflammatory response, disseminated intravascular coagulation and multiple organ dysfunction/injury are established features of heatstroke. However, the mechanisms controlling these alterations are not known. Our Unit is developing various animal models to understand the progression from heat stress to the onset of heatstroke at the molecular and cellular levels. Understanding such events will help identifying novel therapeutic targets. In addition, the Unit is conducting pre-clinical trials to test novel anti-inflammation & anti-coagulation therapies.

Head of Unit:

Mohammed Dehbi, PhD

Members:

Engin Baturcam, MSc

Manal Al-Shike, BSc

Hala Ahmed BSc

Moutassim Al-Sabbahen, BSc

Taher Uz-Zaman, PhD

Deemah Al-Wadaani, BSc

Abderrezak Bouchama, MD

Members:

Goran Matic, DVM

Steve Bobis, DVM

Sahar Salem

Ludivina Apilado

Mohamed Hassan, DVM

RESEARCH PROJECTS

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 017 – 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 published:

- Recombinant activated protein C attenuates endothelial injury and inhibits procoagulant microparticles release in baboon heatstroke. *Arterioscler Thromb Vasc Biol.* 2008 #28:1318-25.

Project Title: Profiling of Heat Shock Proteins Expression in a Baboon Model of Heatstroke.

Investigators: Abderrezak Bouchama, Mohammed Dehbi, Engin Baturcam, 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, 1 abstract were /presented as poster in 2008 at Cold Spring Harbor Laboratories Meeting in New York, USA.

FUTURE RESEARCH DIRECTIONS

Genomic and proteomic profiling of heatstroke in a mouse model (RAC approved project #2070 015). 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.

PUBLICATIONS

- ↪ Bouchama A, et al., (2008). Recombinant activated protein C attenuates endothelial injury and inhibits procoagulant microparticles release in baboon heatstroke. *Arterioscler Thromb Vasc Biol.* #28:1318-25.
- ↪ Roberts et al., (2008). Microvascular injury, thrombosis, inflammation, and apoptosis in the pathogenesis of heatstroke: a study in baboon model. *Arterioscler Thromb Vasc Biol.* #28: 1130-6.

PRESENTATION

- ↪ Dehbi M. et al., (2008). Expression profiling of heat shock proteins in a primate non-human baboon model of heatstroke. The Cold Spring Harbor Lab. Meeting on Cell Stress & Chaperones. New York, USA (Apr. 29 to May 4. 2008).

Laboratory Animal Facility

The mission of the Laboratory Animal Facility (LAF) is to maintain and provide an excellent laboratory animal support services for both clinical and basic research undertaken by scientists, physicians and surgeons of the King Faisal Specialist Hospital and Research Centre and to assist the 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,

The LAF maintains and provides rodents (mice) that are genetically uniform and free from diseases that would compromise the interpretation of research results. In addition, the staff of the facility provides veterinary and technical expertise to various KFSH&RC departments on a daily basis and provides consultation in the safe, humane use of laboratory animals in research and education in compliance with international regulations and KFSH policies.

The LAF is complying with all international & government regulations regarding the use and care of animals in research. All research protocols involving laboratory animals are reviewed by the Animal Care and Use Committee (ACUC).

Head of Unit:

Ra'afat M. El Sayed, DVM, MVSc

Members:

Falah H. Al-Mohanna, DVM, MSc

Goran Matic, DVM

Steve Bobis, DVM

Mohammed Hassan, DVM

Catalino L. Santos

Merfat A. Elyan

Julius D. Maborang

Wilfredo B. Antiquerra

Rolando G. Monzaga

Pio O. Oliveras

Ruben C. Delos Santos

Mona A. Saleh

Bahaa Salem

Baltazar Caducio

AVAILABLE FACILITIES

ANIMAL HOUSING

Currently the facilities house the animals at the King Faisal Specialist Hospital and Research Centre at the:

- LAF (200 square meters) is located at the basement of the RC. Most of animal rooms were converted into laboratories.
 - ∞ Surgical Theatre: includes scrub area for surgeons and surgery room, fully equipped with state of the art surgical equipments.
 - ∞ Microsurgery Animal Lab.
 - ∞ Laparoscopy Training Animal Lab
 - ∞ Animal physiology & pharmacology lab.
 - ∞ Diabetes research & animal behavior facility.
 - ∞ Basic diagnostic lab for animal (hematology, basic chemistry analyzer, coagulation, blood gas).
- An outdoor dog kennels housing 36 individual dogs.
- Indoor Baboon facility (91 square meters), that has two controlled quarantine rooms to house 40-50 baboons during 90 days of quarantine time, negative containment facility, in addition to procedure room, necropsy room, morgue room and cage washing room.
- 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.
- Sheep shelter pen is located adjacent to the outdoor baboon house, has three sections, to house new arrival sheep and post surgery holding area.
- The CCC-LAF is a modern well equipped facility for receiving new small animals, holding, breeding and experimentation and containing 8 animal rooms, each room has 6 cubicles, to house the small laboratory animals such as mice, immunocompromised mice, scid, nude mice, NOD mice and around 25 various strains of transgenic and knockout 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.

RESPONSIBILITIES AND SERVICES

- Provide accredited facilities for housing laboratory animals
- Consult and collaborate with research personnel to assist in project planning and technique development
- Training programs
- Order and receive animals
- Provide daily animal husbandry and health surveillance
- Institutional compliance with animal welfare regulations, standards and policies
- Veterinary and technical support

SERVICE WORK

- Responsible for maintenance, procurement and breeding of a variety of common laboratory animals used in biomedical research and teaching.
- Provide quality services to maintain healthy animals and intervene in control of diseases, diagnosis and treatment of sick animals.
- Enforce professional and international standards set for Laboratory Animal Science practice of providing valuable assistance and advice to physicians and scientists using laboratory animals.
- The Laboratory Animal Facility, Veterinary Care Program provides veterinary care for research and teaching animals housed in KFSH and CCC. This includes preventive health care, routine health monitoring, daily clinical care, and 24-hour emergency service. The staff is available for consultation in a variety of research-specific areas to improve experimental outcome and to help ensure animal welfare throughout the course of the project.
- Provide technical and surgical support services to physicians, researchers and technicians to carry out

animal related work.

- ∞ tissue and tumor transplants
- ∞ thymectomies & Vasectomises
- ∞ bone marrow collections
- ∞ routine immunizations
- ∞ post-surgical care
- ∞ polyclonal, monoclonal and ascites production
- ∞ phlebotomies
- ∞ tattooing
- ∞ ear tagging and implanting transponding microchips animals for identification
- ∞ processing of blood from rabbits, guinea pigs and mice
- Breeding and maintain Nude, SCID, Diabetic, Transgenic and Knock-Out mice.
- Facility for antibodies production and BSL-2 facility for experimentation with infectious and hazardous agents is available at CCC-LAF.
- Special instrumentation of rodents for cardiovascular and hypertension research (Telemetry new technology).
- Cardiovascular and Urological experimentation in large animals and small animals.

CORE ACTIVITIES

Staff at LAF unit facilitate, assist and/or collaborate with researchers of KFSH & RC as well as national and international scientists by providing the following services:

- Advising on the selection and procurement of the appropriate animals for experiments.
- Maintaining and providing appropriate animals to various investigators.
- Training animal users with emphasis on proper handling, care of laboratory animals and basic procedures (blood & tissue collection, dissection and anatomy, anesthesia, euthanasia, pain control and surgical procedures).
- Weekly or on demand, the Animal Facility staff provides blood and tissue samples from laboratory

animal to the Pathology, Microbiology and RC.

- Pre and post-surgical cares
- Housing animals in accordance with the Standard Operating Procedure (SOP).
- Veterinary care such as disease prevention, treatment and vaccination.
- 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

- RAC#2063 013. Signaling pathways involved in heatstroke pathogenesis.
- 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.
- RAC# 2060 039. Modulating the Hypoxia Inducible Factor Signaling Pathways as a Therapeutic Modality to regulate Neovascularization related Retinopathies in mice.

COLLABORATIVE RESEARCH PROJECTS

- RAC# 2020 002. Photo biostimulation: laser effect in wound healing of diabetic & non diabetic rats. Dr. F. Al Watban, Dept. of Biological & Medical Research
- 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
- RAC# 2030 088 Phase I&II. Myocardial Infarct Model in Baboons. Dr. C. Mullangi. King Faisal Heart Institute

- RAC# 2030 057. Investigation of BRAF mutation in thyroid carcinoma from Saudi population in mice. Dr. Y. Shi, Dept. of Genetics.
- 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.
- RAC# 2030 058. Preparation and Characterization of Radiolabeled Bombesin Peptid Analogues for Targeting Human Cancer in mice. Dr. I. Al Jammaz, Dept. of Cycotron and Radiopharmaceuticals (C&R).
- RAC# 2040 027. Synthesis of different radiofluorinated precursors for rapid Production of new PET radiopharmaceuticals. Dr. I. Al Jammaz, Dept. of Cycotron and Radiopharmaceuticals (C&R).
- RAC# 2042 001. Production of 'cold kits' for technetium-99m radiopharmaceuticals. Dr. I. Al Jammaz, Dept. of Cycotron and Radiopharmaceuticals (C&R) in rats.
- 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. Dr. A. Bouchama (Dept. Comparative Medicine part of year).
- 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.
- 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.
- RAC# 2060 039. Modulating the Hypoxia Inducible Factor Signaling Pathways as a Therapeutic Modality to regulate Neo-vascularization related Retinopathies in mice. Dr. Michael DeNiro
- RAC# 2063 013. Signaling pathways involved in heatstroke pathogenesis in two types of mice strains

(mutant and wild strains). Dr. M. Dehbi (Dept. Comparative Medicine).

- RAC# 2070 004. Role of P13-Kinase-AKT pathway in Epithelial Carcinoma in vivo study (Nude /Scid mice.). Dr. Khawla Al Kuraya, Director, RC-KFNCCC&R.

ASSISTANCE PROVIDED TO INVESTIGATORS

- RAC# 2031 088. 7 Baboons. P.I. Dr. Chandra Mullangi
 - ↪ 28 Echo times in 7 baboons
 - ↪ 7 PET/MRI/SPECT times in 7 baboons
 - ↪ 1 Autopsy

COLLABORATION

In addition to our major activity at the level of KFSHRC, our unit collaborates with other national institutions such as: Ministry of Agriculture, King Saud University, National Commission for Wildlife Conservation and Development 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.

FACTS AND FIGURES

In 2008, LAF assisted research and training activities by providing various animals ranging from rodents to primates

This year the LAF produced, and cared for approximately 3,000 mice of various strains and 580 of different rat strains. In addition, approximately 28 New Zealand rabbits, 62 dogs, 70 baboons have been obtained and cared for in the past year. The majority of our inbred mouse strains are produced and maintained in a specific pathogen free (SPF) condition in the cubicle breeding facility at CCC. This facility enables the LAF to maintain

the excellent health status of the mouse colony as well as permit the successful production of large numbers of immuno-compromised scid mice, nude mice, NOD mice and more than 25 various strains of transgenic and knockout mice.

accreditation will both attract and facilitate obtaining research grants and contracts. Moreover, it will add prestige to our Research Centre.

- Training & Education:
 - ⇒ A training course will be offered to the staff of

	Mice	Mice Nude	Mice SCID	Transgenic	Rats	Rabbits	Hamster	Guinea pigs	Dogs	Sheep	Baboons
Used	1280	259	48	X	327	10	X	52	10	0	18
Inventory	493	138	51	558	253	15	24	11	52	2	52
Total	1773	397	99	558	580	28	24	63	62	2	70

TRAINING AND EDUCATIONAL ACTIVITIES

We provide for graduate students, postdoctoral fellows, residents, laboratory technicians, and investigators using the core facilities. Training includes:

- use of anesthetic agents
- surgical techniques
- animal handling and restraint
- animal-related equipment use
- animal tumor models including handling and manipulation of athymic nude rodents
- biosafety and containment operations
- guidelines for animal in vivo use of infectious agents, radioisotopes, carcinogens and toxic chemicals

Breeding colony management services and technical assistance

- breeding
- weaning
- animal identification
- tissue excision for genetic analysis
- breeding and database management implantation

FUTURE PLANS

- 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

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 will 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 to be started to collect the aforementioned materials and books related to Laboratory Animal Science.
- Establishment of small animal procedure room at RC designed for multi-purpose use including routine experimental procedures and performance of rodent aseptic surgery.
- Establishment of small animal imaging program which is of novel imaging approaches to cancer and cancer experimental therapeutics using animal models and pharmacodynamic endpoints. State-of-the-art imaging facilities are extremely expensive and require advanced technical personnel. Modern non-invasive imaging technologies include:
 - ⇒ Magnetic Resonance Imaging (MRI for anatomic, physiologic, and molecular imaging)
 - ⇒ Computed Tomography (CT for anatomic imaging)
 - ⇒ Positron Emission Tomography (PET for metabolic and molecular imaging)

-
- ∞ Optical Imaging (Bioluminescence, Fluorescence)
 - ∞ Ultrasound
 - To Establish a veterinary diagnostic lab: for genetic and health monitoring
 - ∞ It is a part of accreditation for the Animal Facility
 - ∞ Monitor the health condition of lab animals; this is essential for the maintenance of a healthy stock of lab animals, especially, specific pathogen free animals.
 - ∞ Monitor clinical and sub-clinical infections of lab animals.
 - ∞ Diagnostic lab services will facilitate veterinary medical care and will provide complete diagnostic services to the research scientists.
 - ∞ Provide service for fee to the other organizations and agencies such as: Ministry of Agriculture, National Commission of Wildlife and Development, Private Veterinary Clinics, Other animal research facilities.
 - The veterinary diagnostic lab include the following areas:
 - ∞ Hematology
 - ∞ Chemistry and clinical chemistry
 - ∞ Serology
 - ∞ Microbiology & Parasitology
 - ∞ Pathology Services (include histology, gross and microscopic pathology)
 - ∞ With the establishment of a diagnostic laboratory, capable of meeting the increasing demands of the King Faisal Specialist Hospital & Research Center in preparing histopathological sections for microscopic and immunohistochemical tests, the scope of biomedical research will expand dramatically
 - ∞ Genetic analysis.
 - To Establish Animal Physiology and Pharmacology Lab.
 - To Establish Antibody Production Facility.
 - Establish Reproductive Biology and Transgenic Core Facility:
 - ∞ Establish Transgenic and knockout mice Core Facility:
 - Maintain and breed the current transgenic mice strains at LAF-CCC to support biomedical research projects.
 - Establish Transgenic Core Facility to produce transgenic, chimeric and knockout mice for research, many of these animals represent genetic models for human diseases, which will help the researcher to find treatment strategies for such diseases.
 - Produce animal models (Transgenic mice models) for human diseases as for cancer, neuronal degeneration, diabetes, cardiovascular diseases, metabolic diseases etc. Targeted gene disruption → loss of gene function.
 - ∞ To Establish IVF animal lab:
 - Objectives:
 - To promote & improve technical practice and skills
 - To enhance the knowledge of new skills and techniques in IVF
 - To obtain off-springs of sterile animals or animals with low reproductive performance,
 - To study the fertilization mechanisms and to improve the technical skills
 - Embryo and sperm freezing technologies are also important for maintenance of various animals
 - Training in microinjection and embryo transfer technology.
- There are five major steps in the IVF and embryo transfer sequence:
- Monitor the development of ripening egg(s) in the ovaries.
 - Collect eggs.
 - Obtain sperm
 - Put eggs and sperm together in the laboratory, and provide correct conditions for fertilization and early embryo growth.
 - Transfer embryos into the uterus.

Microbial Immunology

Research in the laboratory of Microbial Immunology is currently focused on the host response to 2 major infectious diseases prevalent in KSA, namely Malta fever, and tuberculosis. Elucidation of the regulatory mechanisms involved in microbial pathogenesis and immunity will pave the way towards drug discovery and rational vaccine development. For brucellosis, we found that abundance of TGF- β secretion may underlie the depressed function of T cells in patients with chronic brucellosis (ASM abstract # 08-GM-A-2230-ASM). For TB, however, rigorous experimentations are underway after a daunting experience to secure the patients and controls, *vide infra*.

Head of Unit:

Mohamed G. Elfaki, PhD

Member:

Maaweya Awadalla

RESEARCH PROJECTS

Project Title: Cytokine Responses in Patients With Pulmonary and Extra-Pulmonary Tuberculosis, (RAC # 2030 001; KACST # AT-26-41).

Investigators: Mohamed G. Elfaki, Abdullah A. Al-Hokail

PROJECT DESCRIPTION

Human tuberculosis (TB), one of the most widespread infectious diseases, is the leading cause of death due to a single infectious agent among adults in the world. The disease is commonly caused by *Mycobacterium tuberculosis*, which infects primarily cells of the mononuclear phagocytic system with consequent cellular perturbation and debilitation of the host. Since cytokines are mediators of cell-to-cell interactions, elucidation of their regulatory role is important in understanding the pathophysiology of TB. In this study, we proposed a two-fold approach to investigate the regulatory role of cytokines in patients with tuberculosis. In the first approach, cytokines level in plasma samples of patients with pulmonary and extra-pulmonary TB will be studied by ELISA. In the second approach, the patterns of cytokine gene expression and protein level will be studied *in vitro* by using mononuclear cells as target cells. The threshold detection of cytokines in both systems would provide insights into possible means of immune intervention as well as in the prediction of TB status. Thus, the compendium knowledge of cytokines profile would enhance our judgment about the prognosis of TB and pave the way towards future use of cytokines as adjuvant in the treatment regimen of tuberculosis. Additionally, anticipated differences in cytokine responses between pulmonary and extra-pulmonary TB might be of diagnostic value at certain stages of disease progression.

PROGRESS

The project first, second, and third progress reports had been accepted by KACST scientific committee. Importantly, 2 abstracts (09-GM-A-3487-ASM; 09-GM-A-3497-ASM) have been recently

accepted for presentation at the 109th American Society for Microbiology Meeting which will be held in Philadelphia, PA, U.S.A. during the period from May 17-21, 2009. Briefly, the kinetics of cytokine production in blood of patients with tuberculosis (TB) was assessed by enzyme-linked immunosorbent assay (ELISA) using a panel of monoclonal antibodies specific for each cytokine. At the time of disease diagnosis, none of the cytokines involved in adaptive immunity (IFN- γ ; IL-12) or immune regulation (IL-10) were spontaneously secreted in the plasma of patients with tuberculosis except for TGF- β and traces of IL-4. After 3 months of therapy with antituberculous medications, plasma level of IFN- γ was gradually increased. On the other hand, low production of the cytokines of innate immunity (e.g. TNF- α ,) was noticed in the plasma of patients with pulmonary active tuberculosis. After 3 months of patients' treatment, plasma level of TNF- α was significantly reduced. Further, the cellular production of cytokines in patients with pulmonary active tuberculosis and healthy control subjects was studied in peripheral blood mononuclear cells (PBMC) in response to complex (whole cells, culture filtrate, and cell walls), single secreted (ESAT6, Ag85), or single cytosolic (cytosol F, GroES) antigens of *Mycobacterium tuberculosis* (MTB). Our data showed an enhanced production of TNF- α , IL-10, and IFN- γ by PBMC of TB patients stimulated with complex MTB antigens. Interestingly, an abundant secretion of IFN- γ was noticed in PBMC stimulated with the single antigens, ESAT6 or Cytosol F in comparison to other cytokines. However, negative control subjects showed little or no production of these cytokines. These results suggest that cytokines play a major modulatory role in the outcome of tuberculosis. Furthermore, the enhanced selective production of IFN- γ , but not IL-10, by PBMC stimulated with culture filtrate proteins or cytosolic fraction of MTB suggest that these antigens are potential candidates for the design of subunit vaccines against human tuberculosis.

PUBLICATIONS

- ↪ Elfaki, M.G., Al-Hokail, A.A., Al-Neshmi, A., and Marie, A. (2009). Enhanced expression of growth factors in patients with pulmonary active tuberculosis: associations with disease progression and effect of antituberculous chemotherapy. 109th General Meeting of the American Society for Microbiology, Philadelphia, PA, U.S.A. (May 17-21, 2009). Accepted.
- ↪ Al-Hokail, A.A., Elfaki, M.G., Al-Neshmi, A., and Marie, A. (2009). Production of TNF- α , IFN- γ , and IL-10 by tuberculous peripheral blood mononuclear cells in response to complex and single antigens of *Mycobacterium tuberculosis*. 109th General Meeting of the American Society for Microbiology, Philadelphia, PA, U.S.A. (May 17-21, 2009). Accepted.
- ↪ Elfaki, M.G., and Al-Hokail, A.A. (2008). Enhanced production of TGF- β in patients with chronic brucellosis. 108th General Meeting of the American Society for Microbiology, Boston, Massachusetts, U.S.A. (June 1-5, 2008).

Tuberculosis Research Unit

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.

Head of Unit:

Sahal Al-Hajoj, PhD

Members:

Bright Varghese

Ruba Al-Omari

Mais Al-Herbawi

RESEARCH PROJECTS

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.

Technology of real time PCR DNA Analyzer are being used to detect mutations responsible for resistance.

Project Title: Epidemiology of Drug Resistance TB in Saudi Arabia (KACST approved grant).

Investigators: Sahal Al-Hajoj, PhD, Fahad Al-Rabiah, Riyadh Al-kalif, Sahar Al-Thwadi and Abdullah Al-Dress

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.

Investigators: Sahal Al-Hajoj, PhD, Abdulrhman Al-Rajhi, Fahad Al-Rabiah and Ashraf Attia

PROJECT DESCRIPTION

This project will focus on detection of dormant tuberculosis in a very veruable group of patients. Usually the routine work out for patients undergo renal transplantations is including 100 year ancient skin test

which some times give controversial results and on other occasion does not even detect dormant TB as a results of its low sensitivity.

The moment the patients start receiving immuno-suppressor drugs the dormant TB flare. We are hoping to detect the disease even before start using very specific and sensitive Gold interferon kit.

PROGRESS

This project has been finally approved by Research Advisory Council (RAC) and preparation is underway to start this project.

FUTURE RESEARCH DIRECTION

We are hoping to put together the date 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.

THE DEPARTMENT OF
CYCLOTRON AND
RADIOPHARMACEUTICALS

The Department of Cyclotron and Radiopharmaceuticals

Radiopharmaceuticals are the key components of a viable nuclear medicine practice wherein, on-demand availability is highly essential. Cyclotron and Radiopharmaceuticals Department (C&RD) manufactures and supplies a wide range of radiopharmaceutical products to nuclear medicine centers in the Kingdom, facilitating and enhancing the diagnostic imaging and radiotherapy services.

C&RD performs two distinct functions: Radiopharmaceuticals manufacturing; and Radiotracer Research.

Chairman:

Manhar M. Vora, PhD

Deputy Chairman:

Ibrahim Al-Jammaz, PhD

Administrative Support Staff:

Nora B. D'Souza

Jhonna L. Canicosa

RADIOPHARMACEUTICAL MANUFACTURING

Radiopharmaceuticals are the pharmaceutical products that are labeled with radioactive isotopes, and are the key ingredients in practice of nuclear medicine, either for diagnostic imaging or for therapy. C&R Department is the only facility of this kind within the geographical region manufacturing these specialty products. Moreover, C&R Department has been manufacturing several different cyclotron-based radiopharmaceuticals (diagnostics) for over two decades, and in recent years has added several therapeutic products derived from reactor-based isotopes. Of special interest are the short half-life radiopharmaceuticals labeled with positron emitting radionuclides in support of the most contemporary imaging modality of Positron emission tomography (PET).

Working towards the ultimate goal of establishing the most 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

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 2008

Radiopharmaceutical manufacturing: In the Year 2008, C&R Department's Production Section continued to manufacture and supply radiopharmaceutical products conforming to the 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. Product distribution volume and corresponding revenues increased by 30% primary due to increase in FDG and reinstatement of I-123 based products after refurbishment of the CS-30 cyclotron.

A major expansion project took shape during the year, entailing installation of a 30 MeV cyclotron replacing the aging CS-30 cyclotron which has served well for over twenty five years of continuous operation. Also new line of products are planned, primarily the production of Technitium-99m generators which is a workhorse for diagnostic imaging. Upon completion of the project in May 2010, C&RD will truly become a comprehensive source for 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 radionuclides and radiopharmaceuticals 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.

cyclotron isotopes and radiopharmaceuticals (two are published to-date)

HIGHLIGHTS OF THE ACCOMPLISHMENTS FOR THE YEAR 2008

RADIOPHARMACEUTICALS PRODUCTION RELATED

- 16,133 units of radiopharmaceuticals distribution to 40 nuclear imaging centers in the Kingdom and abroad
- 8,391,796 revenues generated from distribution of radiopharmaceuticals
- 98.5% process success rate in manufacturing radiopharmaceutical products
- Achieved objectives of the ISO 9001:2000 Quality Management System, including customer satisfaction rate of 94.3%.
- 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 to co-author four Guidebooks pertaining to manufacturing

RADIOTRACER RESEARCH RELATED

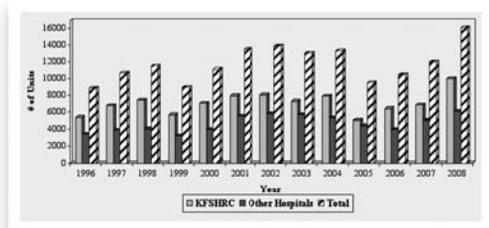
- 10 active research projects
- 4 Grant funds (KACST funded, over 3-4 years)
- 2 publications in peer-reviewed journals
- 10 abstracts and presentations

FUTURE DIRECTIONS

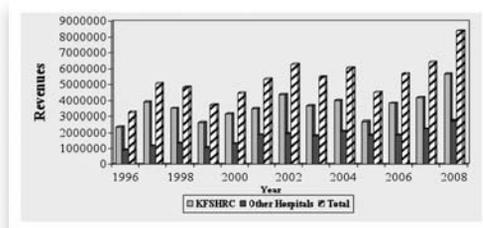
With an ultimate aim of becoming a single source of all radiopharmaceutical needs of the Kingdom, an ambitious project entailing physical expansion of the C&R Department has been initiated. Upon completion of this project, perhaps in May 2010, we expect to achieve our ultimate objective of self-reliance 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
- Installation of Cold Kits manufacturing plant
- Construction of Phase II of the Cyclotron Expansion building

In summary, in the Year 2008, C&R Department continued to perform at par with the previous years, with the notable exception being initiation of the expansion project.



Total Number of Units Distributed
(1996 – 2008)



Total Revenues
(1996 – 2008)

THE DEPARTMENT OF
GENETICS

The Department of Genetics

During 2008 the impact of “program” based research activities and the re-organization of core and service facilities has become evident. The tremendous work of the core facilities, service and administrative sections of the department whilst rarely heralded have been central to the success of many departmental programs. Many scientists have benefited from activities ranging from the extraction of DNA, management of oligonucleotide requirements, genotyping, sequencing and availability of well characterized samples from services such as the newborn screening program. With this foundation the department now has mature and productive programs in 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, Nephrogenetics and Transcriptional Genomics. The research activities of the department are elaborated in specific abstracts that form part of the 2008 annual report. Progress in the service areas continues with growth evident in both the National Laboratory for Newborn Screening and particularly with Saudi Diagnostic Laboratories (SDL). The latter finally attained a long term goal of commercial registration during 2008. Activities of SDL highlight the translational nature of much of the research in the Department of Genetics.

Chairman:

Brian Meyer, PhD

Administrative Support Staff:

This research has underpinned the provision of clinical services including diagnostics, pre-implantation genetic diagnosis, prenatal diagnosis, carrier detection and genetic counseling. The Newborn Screening Program has continued to increase coverage of total births and has together with the molecular genetics laboratory developed a program for carrier detection and prevention; a step further than early detection and intervention. For 2009 we look forward to increasing capacity for core services

such as sequencing and genotyping through automation and adoption of current technologies which include next generation sequencing. This will undoubtedly enhance both research and service capacities of the department and help bring to fruition many novel discoveries currently being embellished by scientists in most programs of the department. Importantly enhancement of the department's capabilities in functional studies are to be a focus for 2009.

Cognitive Genetics (NeuroGenetics)

Advances in molecular genetics are reshaping the perception and practice of neurology, psychiatry, and behavioral sciences. The application of the molecular biology techniques to the study of the nervous system and related fields has greatly accelerated our understanding of the mechanisms involved in biology and pathology of the diseases affecting our bodies. The elucidation of the fundamental causes of the main disorders in these fields has proved to be more intricate; but striking progress is now being made in determining the genetic basis of the diseases of nervous system.

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

Though our unit is recently established, we have initiated several multidisciplinary research projects. Our current projects focus on positional cloning of genes underlying genetic disorders with prominent neurodevelopmental manifestations, mental retardation and detection of chromosomal abnormalities resulting in disruption of nervous system.

Head of Unit:

Dr. Namik Kaya

Members:

Albandary Bin Bakheet MSc

Banan Al-Younes MSc

Nada Abu-Dheim

Jawaher Zehrani

RESEARCH PROJECTS

Project Title: Genetic Basis of Mental Retardation in Families from KSA, RAC# 2080-036.

Investigators: Brian Meyer, Namik Kaya, Talat Wazna, Mohammed Al-Owain, Moeen Al-Sayed, Zohair Al-Hassnan, Hesham Al-Dalan.

PROJECT DESCRIPTION

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

PROGRESS

The project is currently in the start phase in which the samples based on inclusion criteria will be collected.

Project Title: Gene Expression and Immunohistological Finding in Patients With Papillion Lefevre Syndrome, RAC# 2070022.

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

PROJECT DESCRIPTION

Papillon-lefevre syndrome is an autosomal recessive disorder characterized by hyperkeratosis of palm and soles and by a generalized aggressive periodontitis and premature loss of primary and permanent dentition. It is relatively prevalent in a small village north of Riyadh with more than 60 patients being followed in the dental clinic at KFSH&RC. Severe periodontal disease plays an important role in PLS resulting in premature loss of primary and permanent dentition. Two mutations have been identified in the cathepsin C (CTSC) gene in this population. The aim

is to study the histopathology, immunological profile, and gene expression of PLS from blood samples and gingival biopsies; and thus shed more light on the pathophysiology of the disease and explore whether new subclasses of this disease can be identified based on gene expression profiles. Furthermore, we aim to establish a preventative program among this high-risk group through carrier testing and genetic counseling.

PROGRESS

We are in the process of collecting samples.

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 are collected from consanguineous families (affected, unaffected, and parents). Previously collected samples were run on Affymetrix 10K and 500K SNP Mapping Assays. Genomic regions likely to harbor disease causing mutations are under investigation by using fine mapping and targeted gene sequencing techniques.

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, Najj 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 and also establish a CNV database.

PROGRESS

We have collected samples from patients (mainly children) based on our inclusion criteria. We performed high-resolution aCGH using Agilent high-density chips, linkage, CNV, and genome-wide gene expression studies using Affymetrix GeneChip SNP and gene expression assays. We performed the data analysis and obtained initial results. We are currently confirming our results and investigating the allelic frequencies of these CNVs in the Saudi population. We are also in the process of targeting and sequencing the candidate genes from the genome-wide scan analysis, and identify genes or groups of genes underlying the dysmorphic syndromes. One poster was presented in Human Genome Variation Meeting in September 2007, Barcelona, Spain and published in Proceedings of the 9th International Meeting on Human Genome Variation and Complex Genome Analysis, and another poster was presented at the Annual Research Day, KFSHRC, 2008, and multiple manuscripts are under preparation.

Project Title: Hunting for One of the Autism Genes that Might be Linked to Osteopetrosis With renal Tubular Acidosis, RAC # 2030-046.

Investigators: Namik Kaya, Pinar Ozand, Nadia Sakati, Dilek Colak, Ali Al-Odaib, Brian Meyer, Michael Nester

PROJECT DESCRIPTION

This proposal is to investigate patients with osteopetrosis and renal tubular acidosis with autism. A region where carbonic anhydrase 2, the deficient protein in osteopetrosis and renal tubular acidosis is centered will be studied for (a) polymorphic markers using Affymetrix high density SNP chips B) carbonic anhydrase 2 gene mutations; 3) for possible inversion within the region or 4) for possible microdeletion in the region, 5) global

gene expression profiling using Affymetrix's GeneChips. It is anticipated that a gene or genes linked to autism will be thus identified, differences in phenotype will be determined based on gene expression studies and these results should contribute to the research on autism-associated gene markers.

PROGRESS

We have performed gene expression profiling using Affymetrix's Human HG-U133 Plus 2.0 gene expression chips on whole blood RNA from patients and sex and age matching controls. We have identified genes that are common among the autism spectrum diseases. The Principle Components analysis as well as hierarchical clustering clearly classified individuals based on their genetic etiology. Genotyping and mutation screening studies were performed and a novel mutation was found for OPRTA. A manuscript is under preparation.

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, Michael Nester

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, and genotyping experiments were finalized. Currently data analysis and manuscript preparation are ongoing.

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. Linkage experiments as well as fine mapping experiments will also be performed on familial cases.

PROGRESS

We have collected blood from nine patients from different parts of Saudi Arabia. Global gene expression profiling was performed on patients and age and sex matching controls using ABI 1700 system. Initial data analysis was performed by using several statistical and bioinformatics tools. The differentially expressed genes in patients compared to controls have been determined with statistical significance. The unsupervised analysis clearly separated individuals based on their subject group. Functional annotation and biological term enrichment analysis were performed. Also, Linkage studies were performed on familial cases and currently fine mapping and sequencing of targeted genes are ongoing. One poster presented at the Annual Research Day, KFSHRC 2008, and a manuscript is under preparation.

PUBLICATIONS

REFEREED JOURNAL RESEARCH ARTICLES

- ↔ D Colak, N Kaya, J Al-Zahrani, P Muiya, E Andres, N Dzimir, "Left ventricular global transcriptional profiling in human end-stage dilated cardiomyopathy", 2009 (in press, *Genomics*).
- ↔ Kaya N, Imtiaz F, Colak D, Al-Sayed M, Al-Odaib A, Al-Zahrani F, Al-Mubarak BR, Al-Owain M, Al-Dhalaan H, Chedrawi A, Al-Hassnan Z, Coskun S, Sakati N, Ozand P, Meyer BF, "Genome-wide gene expression profiling and mutation analysis of Saudi patients with Canavan disease.", *Genet Med*. 2008 Sep;10(9):675-84.
- ↔ Kaya N, Al-Owain M, Albakheet A, Colak D, Al-Odaib A, Imtiaz F, Coskun S, Al-Sayed M, Al-Hassnan Z, Al-Zaidan H, Meyer B, Ozand P., "Array comparative genomic hybridization (aCGH) reveals the largest novel deletion in PCCA found in a Saudi family with propionic acidemia.", *Eur J Med Genet*. 2008 Aug 26.
- ↔ Shoukri MM*, Colak D*, Kaya N, Donner A, "Comparison of two dependent within subject coefficients of variation to evaluate the reproducibility of measurement devices", *BMC Med Res Methodol*. 2008 Apr 22;8:24. (*co-first author).
- ↔ Alazami AM, Alsaif A, Bohlega S, Al-Semari A, Zlitni S, Alzahrani F, Bavi P, Kaya N, Colak D, Baltus A, Peterlin B, Danda S, Bhatia KP, Schneider SA, Walsh C, Al-Mohanna F, Meyer B, Alkuraya FS, "Mutations in C2orf37, Encoding a Novel Nucleolar Protein, Cause a Multisystemic Disorder of Diabetes, Dystonia, Alopecia and Hypogonadism (Woodhouse-Sakati Syndrome)", *Am J of Hum Genetics*, 2008 Dec;83(6):684-91.
- ↔ Faiyaz-Ul-Haque M, Zaidi SH, Al-Sanna N, Alswaid A, Momenah T, Kaya N, Al-Dayel F, Bouhoagah I, Saliem M, Tsui LC, Teebi AS. A novel missense and a recurrent mutation in SLC2A10 gene of patients affected with arterial tortuosity syndrome. *Atherosclerosis*. 2008 August 5.

RECENT LETTERS IN PEER REVIEWED JOURNALS

- ↪ Kaya N, Al-Odaib A, Rahbeene Z, Al-Hassnan Z, Al-Sharif F, Al-Zahrani F, Colak D, Ozand P, Al-Sayed M. Identification and characterization of mutations in GBA gene causing Gaucher disease in Saudi Patients *Blood, Cells, Molecules and Diseases*, 2008 Sep-Oct;41(2):200-1.

RECENT REVIEW ARTICLES IN PEER REVIEWED JOURNALS

- ↪ Kaya N, Colak D, Ozand P. Autism spectrum disorders: a review. *Trends in Developmental Biology*, 2008, Vol 2, p: 74-94

REFEREED PROCEEDINGS OF MEETINGS

- D Colak , A BinBakheet, B Alyounes, A Al-Odaib, B M Nester, P Ozand, Meyer, N Sakati, N Kaya, "Molecular analysis of osteopetrosis with renal tubular acidosis (OPRTA) subtypes: Classic OPRTA, OPRTA with autism, and OPRTA with mental retardation", Jan. 2009, The Pacific Symposium on Biocomputing, Big Island of Hawaii, USA.
- D Colak, N Kaya, J Al-Zahrani, P Muiya, E Andres, N Dzimiri, "Genome-wide gene expression profiling of human end-stage dilated cardiomyopathy using microarrays", accepted for presentation at HDM-2008 International Conference on Multivariate Statistical Modeling & High Dimensional Data Mining, June 2008, Kayseri, Turkey
- D Colak, MA Chisti, M Goyns, AlBandery B, MM Shoukri, PT Ozand, N Kaya, "Genome-wide gene expression profiling distinguishes early hepatoma from regenerated (and returned to quiescence) and normal liver in young and old rats", invited talk and published in proceedings of HDM-2008 International Conference on Multivariate Statistical Modeling & High Dimensional Data Mining, June 2008, Kayseri, Turkey.

- Kaya N, Colak D, AlBakheet A, Alyounes B, Al-Odaib A, Inan MS, Al-Alwan A, Meyer B, Nester M, Ozand P, Sakati N. Genome-wide gene expression profiling distinguishes osteopetrosis renal tubular acidosis subtypes. The 10th International Human Genome Variation Meeting 2008, October 14-17, Toronto, Canada

LOCAL CONFERENCES AND METTINGS

- Kaya N, Al-Zahrani J, Al-Dosari N, Colak D, Ozand P, Sakati N. Molecular Characterization of a Chromosome 12q Telomeric Terminal Deletion in a Patient with Mosaicism. KFSHRC Annual Research Day, March 16-18, 2009.
- Kaya N, Al-Zahrani J, AlBakheet A, Alyounes B, Al-Owain M, Al-Hassnan Z, Al-Sayed M, Colak D, Inan MS, Al-Odaib A, Meyer B, Ozand P, Sakati N. aCGH using long oligo arrays and SNP based short oligo arrays can be utilized in clinical cytogenetic studies and diagnostics. KFSHRC Annual Research Day, March 23, 2008.
- Kaya N, Colak D, AlBakheet A, Al-Aqeel A, Hassnan Z, Al-Zaydan H, Alyounes B, Al-Rahbene Z, Hashem A, Al-Sayed M, Inan MS, Al-Odaib A, Ozand P, Owain M. A molecular look on early infantile primary lactic acidosis. KFSHRC Annual Research Day, March 23, 2008.
- Kaya N, Colak D, Al-Zahrani J, Al-Owain M, Meyer B, Ozand P. A molecular analysis of a novel compound heterozygote mutation of HEXA gene causing an early age death in a patient from Saudi Arabia. KFSHRC Annual Research Day, March 23, 2008.
- Kaya N, Imtiaz F, AlBakheet A, Colak D, Meyer B, Ozand P. Array CGH reveals the largest novel deletion in PCCA found in a Saudi Family. KFSHRC Annual Research Day, March 23, 2008
- Kaya N, Imtiaz F, Colak D, Al-Odaib, Al-Zahrani F, Al-Sayed M, Al-Mubarak BR, Coskun S, Ozand P, Meyer B, Genome-wide gene expression profiling reveals possible explanations on why canavan patients are having hypotonia and muscle weakness.

- KFSHRC Annual Research Day, March 23, 2008.
- Colak D, Chishti MA, Al-Bakheet A, Ahmad M, Ozand P, Kaya N. Genetic Profile of Early Rat Hepatoma. KFSHRC Annual Research Day, March 23, 2008.
- Colak D, Kaya N, Al-Zahrani J, AlBakheet A, Muiya P, Andres E, Dzimiri N. Left Ventricular Global Transcriptional Profiling in Human End-stage Dilated Cardiomyopathy. KFSHRC Annual Research Day, March 23, 2008

National Laboratory for Newborn Screening (NLNBS)

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 remains twenty four (24) in 2008. As a result, the number of screened newborns by the program increased to approximately one hundred two thousand (102,000). In addition to the newborn screening, the NLNBS conducted about five hundred forty thousand (540,000) specialized tests on specimens of blood, plasma, urine and CSF for follow-up of treatment or from new patients from over two hundred (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.

The NLNBS 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 three hundred thousand (300,000) newborns from two hundred forty (240) birth center in different regions of KSA.

Head of Unit:

Ali Al-Odaib PhD

Members:

Osama Al-Dirbashi, PhD

Ayman Al-Sulaiman PhD

Amal Saadallah, MD, PhD

Mohammad Al-Amoudi

Faisal Al-Otaibi

Fahd Al-Badaoui

Minnie Jacob

Lujane Al-Ahaidib

Ahmad Al-Odaib

Khaled Al-Qahatani

Manhal Al-Mokhadab

Basma Al-Rasheed

Jawaher Al-Saud

Maria Elena Bernabe

Cynthia Laureles

Reham Al-Khininy

Rana Akili

Bindhu Kumari

Ebtesam Jambi

Ebtessam Al-Humaidi

Lolowa Jomaa

Emalyn Samonte

Abdulillah Al-Essa

May Al-Zuhair

Noha Al-Braih

Nouf Al-Khateeb

The program includes screening dried blood spots from newborns at 24-72 hours after birth for sixteen (16) inherited metabolic and endocrine disorders (see list).

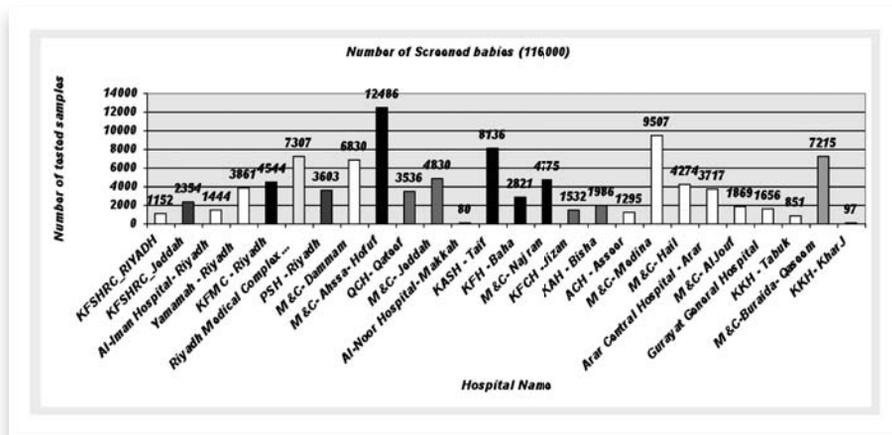
1. Phenylketonuria (PKU)
2. Maple Syrup Urine Disease (MSUD)
3. Arginosuccinase Deficiency (ASL)
4. Citrullinemia (ASD)
5. HMG-CoA Lyase Deficiency (HMG)
6. Isovaleric Acidemia (IVA)
7. Methylmalonic Acidemia (MMA)
8. Propionic Acidemia (PA)
9. Beta-ketothiolase Deficiency (BKT)
10. Methylcrotonyl-CoA 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)

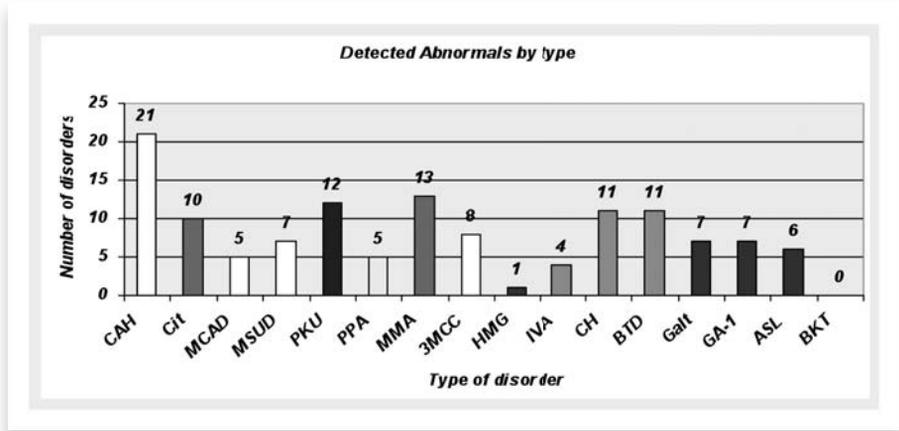
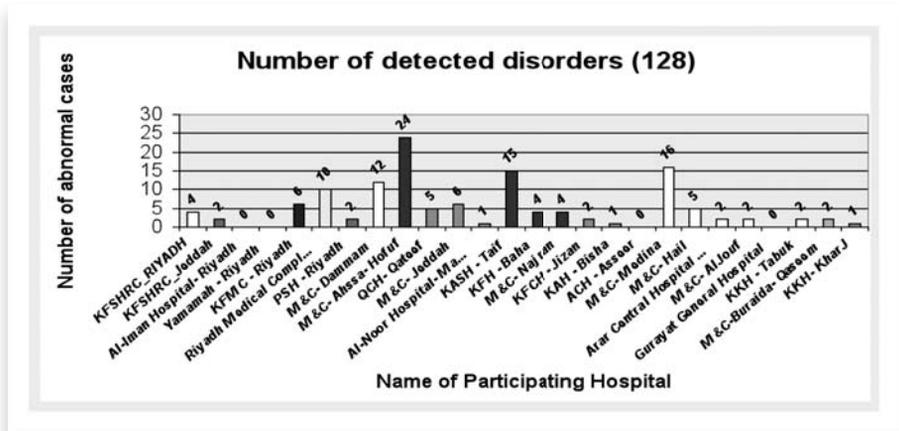
The first twelve (12) of these diseases are screened for by tandem mass spectrometry, the last four (4) disorders

are to be 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, GC-MS, and moor.

PROGRESS

During 2008, the Ministry of Health proposed the increase of samples from 120,000 to 300,000. More than two hundred forty (240) hospitals will participate in this expansion. The program will be administered by Prince Salman Center for Disability Research (PSCDR) and financed and supervised by the Ministry of Health. In 2008, we managed to screen about one hundred two thousand (102,000 babies) and conducted more than five hundred forty thousand (540,000) different tests. More than one hundred twenty eight (128) babies were found to be affected yield an incidence of 1:797. 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 three hundred thousand (300,000) newborns in 2009-2010. This expansion will be combined with extensive campaign for the program in the media.





The First Arabian Hereditary Deafness (FAHD)

The First Arabian Hereditary Deafness (FAHD) Unit was established to study and define the genetics of deafness in Saudi Arabia. Deafness is the most common sensory deficit in human populations (1:1000 child births) with both genetic (50%) and environmental (50%) etiologies. All modes of Mendelian inheritance are observed in deafness, which can be non-syndromic or can be associated with other symptoms (syndromic). Non-syndromic hearing loss transmitted as a recessive trait is the most frequent cause of hereditary deafness and often exhibits the most severe hearing phenotype. Recessively inherited diseases are more prevalent in populations where consanguineous marriages are common, like in Saudi Arabia. The same effect is observed for recessively inherited cases of deafness.

The major objective of the FAHD Unit is to define the genetic basis of autosomal recessive deafness in the Saudi population. To achieve this objective, families segregating profound congenital deafness with an autosomal recessive mode of inheritance will be investigated from across the kingdom as they are a powerful resource for genetic linkage studies of recessively inherited deafness.

Head of Unit:

Faiqa Imtiaz, PhD

Members:

Khushnooda Ramzan, PhD

Danyah Trabzuni

Bashayer Al-Mubarak

Nour Abu-Abed

Abeer Al-Mostafa

Rabab Allam

RESEARCH PROJECTS

Project Title: Role of the DFNB1 locus in Hereditary Deafness Within the Saudi Population, RAC# 2040039 and PSCDR Funded (04-IN-0005-04-EP-1).

Primary Investigators: Dr Khalid Taibah and Dr Faiqa Imtiaz

Co-Investigators: Dr Mohammad Al-Owain

PROJECT DESCRIPTION

Autosomal recessive genes are responsible for about 80% of hereditary non-syndromic deafness of pre-lingual onset. DFNB1, caused primarily by mutations in the GJB2& GJB6 connexin genes are responsible for approximately 50% of pre-lingual, recessive deafness in various populations. Therefore, the role of the DFNB1 locus in hereditary deafness in the Saudi population was investigated as a primary specific aim of this project.

PROGRESS

Upon approval and funding of the project in 2005 through the Prince Salman Center for Disability & Research, patient enrolment commenced in March, 2005. To date, 960 patients/family members have been enrolled in the project. All patients were reviewed by the ENT and Genetics clinics with full clinical and family histories recorded. Several individuals with strong family histories have been identified.

Our results showed that mutations in Connexin 26 (GJB2) account for only 2-5% of patients/family members enrolled in the project; hence DFNB1 is not a cause of hereditary deafness in the Saudi population.

The exclusion of DFNB1 as a major cause of hereditary non-syndromic deafness allowed us to accelerate our efforts with respect to linkage analysis. For our purposes, we require families of 3 or more affected individuals to be able to conduct prioritized linkage analysis using the Affymetrix Gene Chip technology. Results from linkage analysis have identified the gene and disease-causing mutations in a number of families and have provided significant LOD scores leading to candidate gene selection. Identification of the most common forms of hereditary deafness, their incidence and distribution in the Saudi population and application of this knowledge to newborn and pre-marital screening will have a major impact upon early management of hereditary deafness.

FUTURE RESEARCH PLANS

- Expand our collaborative efforts with respect to enrolling families from other institutions in the Kingdom.
- Collaborative studies have been facilitated through a Research Fellowship Award from the Dubai Harvard Foundation for Medical Research to Dr Faiqa Imtiaz with the research laboratory of Professor Cynthia Morton in Harvard Medical School. This collaboration will provide the Unit with direct access to current technologies for rapid sequencing of known deafness genes and provide opportunities for functional studies and expert opinion.

Computational Genetics

The Computational Genetics Section offers collaborative research and services in the areas of research informatics and computational modeling. The staff has experience and expertise in bioinformatics software/database development, customized data analysis, and providing research informatics infrastructure and training.

Head of Unit:

Hanif Khalak

Members:

Recruitment for two (2) engineers in progress

SPECIALTIES INCLUDE BUT ARE NOT LIMITED TO

- Architecture and deployment of high-performance computing infrastructure
- Development of bioinformatics and computational genetics methods, software and databases for data analysis and visualization
- Management of laboratory information systems
- Analysis of high throughput data (e.g.: gene expression, SNP genotyping, metabolic screening, array CGH, DNA sequencing, compound screening)
- Identification of disease phenotype associations to genotype and transcriptional activity
- Annotation of genomic functional and regulatory elements, mapping of pathways, etc

The section collaborates with other research groups within the Department of Genetics, and coordinates with other groups within the Centre and Information Technology Affairs and other KFSH departments contributing to the informatics and computational field.

RESEARCH PROJECTS

Project Title: Establishment of a High-Performance Computing (HPC) Environment and Bioinformatics Portal for Research Genetics.

Investigators: H.G. Khalak, B.F. Meyer, W. Khayyat (ITA), W. Hossari (ITA)

PROJECT DESCRIPTION

The Computational Genetics Section of the the Department of Genetics has architected and deployed a High-Performance Computing (HPC) system and environment to support large-scale bioinformatics analyses for projects within the Research Centre. The HPC infrastructure provides a total computational power of 100+ CPUs, 240GB of RAM memory, and 20TB+ of high-performance disk storage.

This prodigious computing capacity will enable the processing of the large datasets from whole genome genotyping, expression microarrays, DNA and protein sequence analysis, and image processing that contributes to many of the research projects within the department and the Research Centre. Scientific applications such as MATLAB, BioConductor, DNASTar, ClustalW, and Sequencher allow many scientists to simultaneously perform rapid computing tasks on their experimental data to efficiently achieve results that would otherwise take an order of magnitude more time, and in many cases would not be possible on workstation computers.

The computing capacity is also being deployed to establish the Middle East mirror site for the UCSC Genome Browser, which is used by thousands of scientists through the world, including many in the Middle East. Collaborations with other units in the Research Centre will provide an aggregate computing resource to support larger-scale analyses to push the boundaries of science at KFSH&RC.

PROGRESS

The hardware infrastructure, including the computing and storage server systems are now in place and configured for high-performance computing

capability. Database, web, and scientific computing applications such as described above are being deployed, and large-scale dataset mirroring is underway. Individual core lab workflows are being tested to utilize the new infrastructure and will soon migrate their production tasks to adopt these workflows.

Project Title: National Laboratory for Newborn Screening (NLNBS) LIMS Infrastructure.

Investigators: H.G. Khalak, A. Al-Odaib, O. Al-Dirbashi, P. Siddiqui (BESC), F. Badoui

PROJECT DESCRIPTION

The Newborn Screening Program aims to provide total coverage of all newborns in the Kingdom, and therefore requires a high-availability computing infrastructure to ensure reliably continuous uptime to facilitate the constant throughput of samples from its network of health institutions (over 400 samples daily). This requirement involves aspects which provide redundancy and quick recovery at a number of levels:

1. Hardware : lab computer systems (LIMS) → clustered servers
2. Network : cables and switches (Ethernet and Fiber Optic) → redundancy
3. Data : disk and database level-mirroring → redundancy and backups

The NLNBS requires a LIMS that runs on a well-functioning and high-availability computing system. A number of discussions over the past month or so with the vendor (Perkin-Elmer, PE) have yielded several successive specifications of the architecture of this system to meet the needs of the laboratory projects and scientists. Architecture specifications at various stages of the project have attempted to achieve these aims within the constraints of the Research Centre (RC) and the Hospital generally, mainly involving Information Technology Affairs (ITA). This work aims to fulfill

the requirements to establish a LIMS according to the NLNBS specifications.

PROGRESS

Currently (04-09), the PE LIMS has been installed by the vendor and is being tested and used by the NLNBS team within their assays workflows. Standard Operating Procedures (SOPs) are being established with respect to operation, maintenance, and recovery of the LIMS systems and application in accordance with the requirements specified above.

Project Title: Calculating Age of Founder Mutations.

Investigators: H.G. Khalak, F. Al-Kuraya, A. Al-Azami, L. Safieh

PROJECT DESCRIPTION

Many Mendelian diseases can be associated with a single mutation within a given population, that arose in the past in a single founder individual or group from whom the population descended. Phylogenetically, the haplotypes existing in the population of affected individuals differ to varying degrees from the founder haplotype form which they were derived through recombination and other molecular processes. It was the purpose of this study to implement and apply techniques to calculate, given a sample of haplotypes for a disease locus, the age of the founder mutation. Recent work by Genin et al (2003) and others have proposed methods to calculate the number of generations required to yield the most-likely recombination events that would explain a given set of haplotypes generated by a common founder.

PROGRESS

An algorithm in Genin et al (2003) was implemented from scratch and applied to a set of haplotypes around the C2orf37 locus acquired in a study of Woodhouse-Sakati Syndrome patients, leading to a contribution to a published article. In addition, code implementing an enhanced version of the algorithm was obtained and is being used for similar age of mutation analyses.

Project Title: Haplotype Analysis for Case-Control Association Studies.

Investigators: H.G. Khalak, G. Mohamed, N. Dzimir.

PROJECT DESCRIPTION

The overwhelming majority of genetic association studies conducted in the context of common diseases analyze the correlation between presence/absence of specific (SNP) marker genotypes within a case-control context. The power of these studies can often be improved by combining multiple, ordered markers into haplotypes which can subsequently also be analyzed for association between case and control groups. We have identified and applied a number of techniques for haplotype association analysis to studies investigating loci implicated in coronary artery disease (CAD) and myocardial infarction within Saudi patients.

PROGRESS

Analyses of association at the level of allele, genotype, and haplotype have been conducted for CAD and MI patient data for markers within and nearby the PSMA6 locus. Successful application of modules within the SAS, SPSS, and R software packages has contributed to articles submitted for publication, including the identification of haplotypes which were common between CAD and MI phenotypes.

Project Title: Bioinformatic Analysis of H5N1 Avian Flu Viral Strains from Saudi Isolates in the Context of a Global Epidemic.

Investigators: H.G. Khalak, A. Al-Qahtani (BMR), A. Al-Ahdal (BMR)

PROJECT DESCRIPTION

Global pandemic influenza infections are a major concern in recent and coming years, particularly in the domestic fowl industry in the Kingdom and worldwide. Of crucial importance is the spread of highly pathogenic viruses such as H5N1 from bird to human. Recent outbreaks of H5N1 infection within Saudi bird stock prompted investigation of the nature and epidemiology of

the infections. This study undertakes to identify possible sources of H5N1 infection and concomitant risk profiles of Saudi viral strain infection within avian and human populations.

PROGRESS

Viral isolates of H5N1 strains from 40+ samples of birds in the Kingdom have been extracted, processed, and sequenced. All data from these samples have been collated, and DNA sequence analysis using ChromasPro and DNASTar tools has been performed to identify the HA and NA sequences for each individual isolate. Multiple Sequence Analysis (MSA) using the CLUSTALW software was done to perform an intrinsic study of the Saudi isolates, wherein two main distinct clades were discovered. A large-scale phylogenetic analysis was conducted aggregating with 1300+ other isolates from the NCBI Influenza database, and the Saudi isolates (except for 2 outliers) occupied a distinct sub-clade within Clade 2.2 in the WHO nomenclature, as expected. We are in the process of performing followup studies including further bioinformatic analyses at the DNA and protein level. A manuscript is being prepared to submit for publication.

PUBLICATIONS

REFEREED JOURNAL RESEARCH ARTICLES

- ↪ Alazami AM, Alsaif A, Bohlega S, Al-Semari A, Zlitni S, Alzahrani F, Bavi P, Kaya N, Colak D, Khalak H, Baltus A, Peterlin B, Danda S, Bhatia KP, Schneider SA, Walsh C, Al-Mohanna F, Meyer B, Alkuraya FS, "Mutations in C2orf37, Encoding a Novel Nucleolar Protein, Cause a Multisystemic Disorder of Diabetes, Dystonia, Alopecia and Hypogonadism (Woodhouse-Sakati Syndrome)", *Am J of Hum Genetics*, 2008 Dec;83(6):684-91.
- ↪ Alsmadi O, Muiya P, Mohamed G, Meyer B, Al-Saud H, Al-Mohanna F, Alshahid M, Khalak H and Dzimir N, "The Proteasomal Alpha Subunit Type 6 and KIAA0391 Gene Cluster confers risk for Myocardial Infarction", submitted to *Am. J. of Med. Gen.*

LOCAL CONFERENCES AND MEETINGS

- ↪ Khalak H.G., Meyer B.F. Establishment of a High-Performance Computing (HPC) Environment and Bioinformatics Portal for Research Genetics. KFSH&RC Annual Research Day, March 16-18, 2009.

TRAINING COURSES

- ↪ Series in Computational Genetics Analysis (CGA)
- ↪ 19/01/2009 CGA 101: Mapping Markers, CNV and LOH
- ↪ 05/03/2009 CGA 201: Linkage Analysis
- ↪ 26/03/2009 CGA 301: Association and Regression

Developmental Genetics

The unit is focused on the study of the roles played by genes in the normal human development. The strategy of the unit is to study genes that result in various developmental defects (also known as birth defects) in humans as a proxy to normal development. Given our existing expertise, our focus in the short terms has been on craniofacial and eye development with two major RAC approved projects for each of the two body areas.

Head of Unit:

Fowzan AlKuraya, MD, FAAP, FACMG

Members:

Mohammed AlDahmesh, PhD

Anas Alazami, PhD

Leen AbuSafieh, PhD

Mohamed Al-Dosari, PhD

Fatima AlZahrani

Tarfa AlShidi

Ranad Shaheen

Hanan Shamseldin

Mais Omar Hashim

CRANIOFACIAL DEVELOPMENT

This body area is highly complex in its development which explains its frequent involvement in a wide array of genetic disorders. Our lab was the first to describe mutations in *C2orf37* as causative to Woodhouse-Sakati syndrome, a neuro-ectodermal-endocrine disorder with craniofacial involvement and we've made significant progress in the functional characterization of the gene product, a novel nucleolar protein with wide expression profile. The mouse model for this disorder is being made which will allow us to better annotate this novel protein in an ideal developmental context. We have also identified mutations in *SCYL1BP1* as causative of Geroderma Osteodysplasticum although our report will come second as another group published this result toward the end of our analysis. In addition, our use of molecular karyotyping as a tool to study patients with craniofacial dysmorphism has generated a number of interesting observations that we're still accumulating. Intriguingly, we have just identified the gene responsible for a very rare autosomal recessive disorder characterized by midline nasal cleft and renal agenesis and work is underway to further characterize the developmental role of this gene. We will continue our strategy of using patients with craniofacial anomalies as a proxy to the study of normal development of that body system.

EYE DEVELOPMENT

The highly organized optical system of the eye is under tight developmental control. Indeed, early work on the developmental genetics of the eye has set the stage for the study of developmental genetics of other organ systems. With our wide network of collaborators, we have been able to recruit patients with myriad genetically determined eye anomalies. We have published the largest series from the Middle East with congenital hereditary endothelial dystrophy of the cornea and established that the disease appears to be genetically homogeneous. We have made the intriguing observation of the occurrence of autosomal recessive form of cataract secondary to

CRYAB mutations. Still in the anterior segment, we're soon going to publish our experience with anterior segment dysgenesis in Saudi Arabia including the identification of novel copy number variants and loci. In the retina, we have recently identified the minimal linkage interval for a highly interesting retinal vascular anomaly called familial retinal arterial microaneurysm (FRAM) and work is underway to identify the culprit mutation. Both syndromic and nonsyndromic retinal dystrophy have been studied extensively in our lab. Other than being able to use homozygosity mapping to quickly and efficiently identify a wide array of founder as well as private mutations for this genetically heterogeneous eye disorder, we have been proactive in the empowering our patients to benefit from the knowledge of their mutations to pursue reproductive options not otherwise available to them.

PUBLICATIONS

- ↪ Aldahmesh MA, Abu-Safieh L, Khan AO, Al-Hassnan ZN, Shaheen R, Rajab M, Monies D, Meyer BF, Alkuraya FS. Allelic heterogeneity in inbred populations: the Saudi experience with Alström syndrome as an illustrative example. *Am J Med Genet A*. 2009 Feb 15;149A(4):662-5.
- ↪ Aldahmesh MA, Al-Hassnan ZN, Aldosari M, Alkuraya FS. Neuronal ceroid lipofuscinosis caused by MFSD8 mutations: a common theme emerging. *Neurogenetics*. 2009 Mar 10. [Epub ahead of print].
- ↪ Alazami AM, Al-Saif A, Al-Semari A, Bohlega S, Zlitni S, Alzahrani F, Bavi P, Kaya N, Colak D, Khalak H, Baltus A, Peterlin B, Danda S, Bhatia KP, Schneider SA, Sakati N, Walsh CA, Al-Mohanna F, Meyer B, Alkuraya FS. Mutations in *C2orf37*, encoding a nucleolar protein, cause hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal syndrome. *Am J Hum Genet*. 2008 Dec;83(6):684-91. Epub 2008 Nov 20.
- ↪ Al-Dosari MS, Al-Muhsen S, Al-Jazaeri A, Mayerle J, Zenker M, Alkuraya FS. Johanson-Blizzard syndrome: report of a novel mutation and severe liver involvement. *Am J Med Genet A*. 2008 Jul 15;146A(14):1875-9.

- ↔ Alazami AM, Alzahrani F, Alkuraya FS. Expanding the "E" in CHARGE. *Am J Med Genet A*. 2008 Jul 15;146A(14):1890-2.
- ↔ Mohammed A. Aldahmesh, Arif O. Khan, Brian F. Meyer, Fowzan S. Alkuraya. Mutational Spectrum of SLC4A11 in Autosomal Recessive CHED in Saudi Arabia. *Inv Opth Vis Sci* (In Press).
- ↔ Abu Safieh L, Khan AO, Alkuraya FS. Identification of a novel CRYAB Mutation Associated with Autosomal Recessive Juvenile Cataract in a Saudi family. *Mol Vis* (Submitted).
- ↔ Arif O. Khan, Mohammed A. Aldahmesh, Saeed Al-Ghedan, Brian F. Meyer, Fowzan S. Alkuraya. Corneal decompensation in recessive cornea plana. *Opth Gen* (Submitted).

Saudi Diagnostic Laboratory

During 2008 the main focus of Saudi Diagnostic Laboratories (SDL) remained on the translational use of Research Programs within the Department of Genetics for the provision of molecular diagnostic services for patient care. During 2008 SDL was re-accredited by the College of American Pathologists for the third time. The laboratory has now operated under this accreditation for over 5 years. SDL has made additional progress in understanding the molecular basis of a large number of Mendelian diseases and continues to identify Arab specific mutations for these disorders. A good indicator of this is in respect of inborn errors of metabolism where 39 genes are currently screened, 125 mutations have been encountered, 55 of which are novel and likely to be unique to the Arab world.

Head of Unit:

Brian Meyer, PhD

Members:

Nabil Moghrabi, PhD

Amr Al-Saif, MD, FACMG

Dorota Monies, PhD

Mohammed Al-Hamed, MSc

Rana Al-Amr, MSc

Raeesa Delaignan, BSc

Ala Doubi, BSc

Nouran Al-Saud

Ola Khashoggi

SDL now performs a repertoire of over 100 tests many of which are unique to its operation. Through these activities the KFSHRC is becoming increasingly independent in molecular genetic testing. SDL was the first regional laboratory to introduce molecular karyotyping, an area that will add substantial diagnostic power for investigation of sub-microscopic chromosomal aberrations. SDL has continued its activities in the area of animal genetics where it has processed over 1000 samples for parentage verification of Arabian horses.

SDL provides diagnostic services for many clinical departments and sections at KFSHRC. These include,

Medical Genetics, Pediatrics, Neurosciences, Obstetrics & Gynaecology, Pediatric Immunology and Pediatric Nephrology among others. During 2008 over 1500 diagnostic tests were performed by SDL in support of these services. Importantly the capabilities of SDL have facilitated preventive medicine through carrier detection, pre-implantation genetic diagnosis and prenatal testing. Prenatal testing has increased from 4-5 per year to 1-2 samples per week during the course of 2008. SDL continues to expand its repertoire of testing and will focus its attention on delivering services more widely throughout the kingdom in 2009.

Genotyping Core Facility

The main aim of this unit is to provide genotyping for DNA Analysis and expression profiling using the Affymetrix GeneChip technology, accelerating the genetic research and enables the researchers to develop the diagnostic tools and tailor treatments for individual patients by identifying and measuring the genetic information associated with mendelian and complex disorders. The data generated from the core facility is used for linkage analysis, population studies, Cytogenetic research, and differential gene expression. With the help of four fluidics GeneChip Stations this year, the core facility processed 1500 Genchip arrays for 250K, 212 samples for SNP 6.0 which includes 1 million SNPs and 400k non-polymorphic probes for copy number variation analysis/LOH. For the RNA profiling, 100 samples were processed for U133 expression and 30 samples were processed for Human ST 1.0 arrays.

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

Head of Unit:

Salma Wakil, PhD

Members:

Batool Baz, MSc

Rasha Ramadan, BSc

Samiya Hagos, BSc

RESEARCH PROJECTS

Project Title: Mapping of X-linked Diseases With Mitochondrial Abnormalities.

In this project whole genome scanning was done using affymetrix 250styI for the family of three affected cases. Based on linkage results sequencing of the FGD1 gene which encodes Rho/Rac guanine exchange factor (GEF) was done. A nonsense mutation was identified in all affected individuals fully consistent with an X-linked pattern of inheritance.

Project Title: Clinical and Molecular Characterization of Patients With Inherited Arrhythmogenic Disorders.

This project is in collaboration with pharmacogenetics unit where the candidates genes involved for LQT and other arrhythmogenic disorders are screened and whole genome scanning is done for 2 families.

Project Title: Localization of Familial Juvenile Rheumatoid Arthritis.

The objective of this study is to perform Homozygosity mapping and use positional candidate gene approach to identify the gene underlying this novel syndrome. So far based on the four families we performed the whole genome scan using affymetix arrays, we identified a homozygous region on chromosome 13 for all the affected individuals. We identified a novel mutation in a novel gene for this disorder. Functional studies are ongoing to study the disease mechanism for this novel gene with unknown function.

Project Title: Identifying the Chromosomal Location of the Gene Underlying a Novel Autosomal Recessive Syndrome of Myopathy.

The objective of this study is to determine the chromosomal location for the gene causing autosomal recessive myopathy. Using 250 mapping arrays for the whole genome scans, identified homozygous regions which harbours candidates genes. Presently we are screening the genes to identify the variations which might be linked to this disorder.

Gene Therapy

Gene Therapy Unit is currently conducting experimental gene therapy research on thyroid cancer, elucidating molecular defects leading to thyroid tumorigenesis, and molecular genetic analysis of genes involved in endocrine disorders. Significant progress has been made on 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, aberrant splicing, and its pseudogene activation in thyroid tumors from Saudi population. *BRAF*^{V600E} mutation, aberrant splicing 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- α 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.

Head of Unit:

Yufei Shi, PhD

Members:

Minjing Zou

Essa Baitei

Roua Al-Rijjal

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.

PROJECT 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/IL-12 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 V600E 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 RT-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^{V600E} 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.

In a parallel study, we investigate aberrant *BRAF* splicing and its association with *BRAF* mutation in 68 thyroid tumors. Novel *BRAF* splicing variants were detected in 12 PTCs, 3 FVPTCs, and 1 ATC, as well as in two thyroid carcinoma cell lines ARO and NPA. These variants did not have N-terminal autoinhibitory domain of wild-type B-Raf, resulting in an in-frame truncated protein that contained only C-terminal kinase domain and caused constitutive activation of B-Raf. These variants were significantly associated with advanced disease stage and *BRAF*^{V600E} mutation ($p < 0.001$, Fisher exact test). Furthermore,

expression of these variants in NIH3T3 and CHO cells could activate MAP kinase signaling pathway, transform them *in vitro*, and induce tumors in nude mice. These data suggest that *BRAF* splicing variants may function as an alternative mechanism for oncogenic B-Raf activation. Combination of *BRAF*^{V600E} mutation and its splicing variants may contribute towards disease progression to poorly differentiated thyroid carcinoma.

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- α 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 dexamethason. 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- α 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.

PUBLICATIONS

- ↔ Cannabinoid CB2 receptor induction by IL-12 and its potential as a therapeutic target for the treatment of anaplastic thyroid carcinoma Shi Y, Zou MJ, Baitei E, Al-zahrani A, Parhar RS, Al-Makhalafi Z, and Al-Mohanna FA. *Cancer Gene Therapy*. 15:101-107, 2008.
- ↔ Genotype – Phenotype Correlation in a Family with Primary Cortisol Resistance: Possible Modulating Effect of the ER22/23EK Polymorphism. Raef H, Baitei EY, Zou MJ, and Shi Y. *Eur J Endocrinol*. 158: 575-581, 2008.
- ↔ Radioiodinated naphthylalanine derivatives targeting pancreatic beta cells in normal and non-obese diabetic mice. Amartey J K, Shi Y, Al-Jammaz I, Esguerra C, Al-Otaibi B and Al-Mohanna F. *Experimental Diabetes Research*. 2008:371716, 2008.
- ↔ Diagnosis by Serendipity: Cushing Syndrome Attributable to Cortisol-Producing Adrenal Adenoma as the Initial Manifestation of Multiple Endocrine Neoplasia Type 1 due to a Rare Splicing Site Men 1 Gene Mutation. Alzahrani, A, Al-Khaldi N, Shi Y, Al-Rijjal RA, Zou MJ, Baitei EY, Amin T. *Endocr Pract*. 14:595-602, 2008.
- ↔ *BRAF*^{V600E} mutation and oncogenic activation of MAP kinase by its pseudogene in thyroid tumors. Zou MJ, Baitei E, Al-zahrani AS, Al-Mohanna FA, Farid NR, Meyer B, and Shi Y. *Neoplasia* 11:57-65, 2009.
- ↔ Aberant *BRAF* splicing as an alternative mechanism for oncogenic B-RAF activation in thyroid carcinoma. Baitei E, Zou MJ, Al-Mohanna F, Collison K., Al-zahrani AS, Farid NR, Meyer B, and Shi Y. *J Pathology* 217:707-715, 2009.

Transcriptional Genetics

The broad field of interest, in the transcriptional genetics section, is the chromatin and transcriptional regulation of genes that regulate the immune system function and development. Disregulation of any the immune system can lead to many debilitating diseases such as immune deficiencies, cancer and auto-immunity. We have been focused on the regulation of the T-Cell receptor alpha and delta ($TCR\alpha/\delta$) gene locus and on the role of $ROR\gamma_t$ transcription factor in controlling T-cell development and its role in protecting us from developing auto-immune diseases and cancer. Our unit is one year old. However, during this year we have characterized 5 promoter elements within the $TCR\alpha/\delta$ locus that control the expression and recombination events during the T-cell development within the thymus. In the coming year we will continue to study the chromatin and transcriptional regulation of the $TCR\alpha/\delta$ locus as described in the RAC-approved research project. Moreover, we will initiate the $ROR\gamma_t$ RAC approved project.

Head of Unit:

Brian Meyer, PhD

RESEARCH PROJECTS

Project Title: Transcriptional Regulation of TCR α / δ Locus, RAC# 2080 019.

Investigators: Dr. Abbas Hawwari, Dr. Goran Matic, Dr. Edward Hitti, Dr. Peer Mohideen Abubucker, Dr. Mohamed Elkhalfifa

PROJECT DESCRIPTION AND PROGRESS

Humeral immunity depends on the generation of diverse repertoire of immunoglobulin (Ig) and T-cell receptor (TCR). For this to happen, mature Ig and TCR genes are generated by the rearrangement of one of each of the Variable (V), Diversity (D), and Joining (J) gene segments by the process of V(D)J recombination. Each gene segment is flanked by Recognition Signal Sequences (RSS). This process occurs during lymphocyte development, as well as in response to exogenous stimuli and it is tightly controlled, so that it is restricted to the appropriate cell lineage and stage of development. Recombination is initiated by DNA breaks mediated by Rag1 and Rag2 proteins at two RSS borders which the normal rejoining process resolves both sets of DNA ends efficiently. Failure of the normal rejoining triggers cellular DNA damage sensors leading to cell death and the prevention of oncogenic transformation. Impairment of these responses may allow alternative DNA repair pathways to mediate rejoining of antigen receptor genes with sites elsewhere in the genome. This breach on DNA integrity may lead to lymphoma-associated chromosomal translocations, which is a central feature of neoplasms in the immune system such as non-Hodgkin's lymphoma (NHL) and acute leukemia. NHL translocations involve the antigen receptor loci which place structurally intact T-cellular proto-oncogene under the regulatory influence of the Ig or TCR genes leading to effects on cell growth, cell differentiation, or apoptosis. Moreover, evidence suggest that NHL translocations arise from errors in the normal V(D)J recombination. As an example, the t(7;9) (q34;q32) translocation of T-cell lymphoblastic lymphoma/leukemia involves breakpoints

at RSS flanking D segments of the TCR β gene on chromosome 7. Another example of the involvement of TCR rearrangement in disease is cutaneous T-cell lymphoma (CTCL) which is a clonal expansion of T-cells. Specific TCR rearrangements found in CD8⁺ cytotoxic T-cell infiltrate in skin biopsies from patients with CTCL have been correlated with clinically benign course of the disease. These patients have lower CD4⁺ T-cells and malignant T-cells. On the other hand, patients with poor prognosis and with advanced stages of the disease have more malignant T-cells and more CD4⁺ T-cells than CD8⁺ T-cells suggesting that certain TCR rearrangements are protective against CTCL. So, it is critically important to understand the normal regulation of V(D)J recombination at the molecular level in order to understand the safe mechanism employed by cells to prevent translocation and hence preventing transformation. It became very clear in the last few years that V(D)J recombination is regulated at the level of gene transcription and chromatin structure. To do that we have been characterizing five promoter elements that associate with different gene segments and dictate at what stage of T-cell development these segments are activated.

Project Title: ROR γ t Role in T-Cell Development, Autoimmunity and Transformation, RAC # 2080 046.

Investigators: Dr. Abbas Hawwari, Dr. Namik Kaya, Dr. Dilek Colak, Dr. Goran Matic, Dr. Naji Al-Dosari

PROJECT DESCRIPTION AND PROGRESS

ROR γ t, a member of the hormone nuclear receptor super family, is a transcription factor that activates or suppresses many genes. The function of ROR γ t was studied in multiple mouse models that are deficient in ROR γ t. ROR γ t^{-/-} mice lack both ROR γ t and ROR γ t (an isoform variant of ROR γ t) and ROR γ t^{GFP/GFP} mice (do not express ROR γ t but express EGFP instead). These mouse models showed that ROR γ t expression

is restricted exclusively to a limited number of cell types in the immune system, specifically; double positive (DP) thymocytes, lymphoid tissue inducer (LTI), crypto patches (CP), isolated lymphoid follicles (ILF), and T helper -17 (Th17) cells. ROR γ t was shown to be indispensable for the development of secondary immune organs such as Peyer patches (Pp), and lymph nodes (LN). Other defects due to ROR γ t loss are also observed: proliferation/apoptotic defects in DP thymocytes, inefficient DP thymocytes development, lack of CP and ILF, enlarged spleen and absence of Th17 cells. Moreover, ROR γ t is involved in the development of autoimmune diseases and thymic lymphoma. Our knowledge of the molecular mechanism by which ROR γ t controls the development of immune cells, organs and structures and protect against autoimmunity and thymic lymphoma

is lacking. We think that in order to understand these processes, we need to understand: first, what controls ROR γ t expression and why it is restricted to only small numbers of immune cell types, second, the genes that are regulated by ROR γ t and third, what proteins interact with ROR γ t to facilitate its function. This knowledge will help us understand, not only the development of DP thymocytes, LN, Pp, CP, ILF, and Th17, but also the process by which ROR γ t protects us against autoimmune and lymphoma diseases. On the long run, this information will help in the diagnosis, drug design and treatment of such diseases in a similar fashion to the success story with estrogen receptor and breast cancer. We have just started on this project and we currently doing the necessary cloning and developing reagents such as antibodies.

Cardiovascular and Pharmacogenomics Research Unit

RESEARCH PROJECTS

Project Title: Evaluation of the Relevance of Single Nucleotide Polymorphism for Coronary Artery Disease in the Saudi Population, Project 2010020.

Investigators: Nduna Dzimir, Futwan Al-Mohanna, Maie Al-Shahid and Brian Meyer

Head of Unit:

Nduna Dzimir, PhD

PROJECT DESCRIPTION

This study looks at the role of mutations in candidate genes for the risk of coronary artery disease (CAD) using the Saudi population as a study model. We intend to first identify SNPs in the population and then evaluate their role in predisposing individuals to acquiring the disease.

PROGRESS

Following the identification of SNPs in several genes of interest by sequencing, we embarked on association studies using real-time PCR procedures for a number of these genes. Thus far, we have accumulated data on the peroxisome proliferator-activated receptor α/β , proprotein convertase subtilisin/kexin type 9, paraoxonase, myocyte enhancer factor-2 and human endothelial transcription factor GATA2 in relatively large populations (<2000 individuals). This data is currently being analyzed for association with CAD, and outcomes should be due for publication in the coming months.

Project Title: Relevance of Lipid Metabolizing Proteins in the Treatment of Hypercholesterolemia and Coronary Heart Disease, Project # 2030012.

Investigators: Nduna Dzimiri, Futwan Al-Mohanna, Maie Shahid and Brian Meyer

PROJECT DESCRIPTION

The project endeavours to establish possible association of mutations in candidate genes with variations in the way individuals respond to statin (lipid lowering agents) therapy of hypercholesterolaemia in a target population of about 3,000 patients. These genes include 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), cholesteryl ester transfer protein, Liver X receptor, cytochrome P450 subtype CYP3A4, receptor alpha subtype gene, sterol regulatory element-binding protein subtype 2 and the SREBP cleavage-activating protein.

PROGRESS

Recruitment of the required population size is still in progress. However, during the report period, we initiated the study on the HMGCR both as a cause of the disease and in relation with differential response to statin therapy. In all, we are targeting nine SNPs that we identified in the Saudi population, seven of which are novel. To date we have accomplished complete genotyping in <2500 individuals. Preliminary analysis indicates an association of a haplotype derived from four of the SNPs with manifestation of the disease.

Project Title: Clinical and Molecular Characterization of Patients With Inherited Arrhythmogenic Disorders, Project # 2050035.

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

PROJECT DESCRIPTION

This study aims at identifying genes associated with familial arrhythmogenic disorders including the long QT syndrome (LQTS), Brugada and Sinus sick syndrome, in the Saudi population. We target some 12 genes that are either known to cause or to be associated with these syndromes. This information should be utilizable for diagnostic and prophylactic strategies in the management of patients with arrhythmogenic disorders.

PROGRESS

To date 5 families with more than 7 members each and four with at least one affected and (un) affected siblings have been recruited. So far, we have sequenced the exon and exon-intron junctions of the potassium voltage-gated channel, KQT-like subfamily, member 1 (KCNQ1), potassium voltage-gated channel, subfamily H (eag-related), member 2 (KCNH2) and sodium channel, voltage-gated, type V, alpha subunit (SCN5A) genes, and data is being analyzed. 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.

Hereditary Immunology Unit

There are wide varieties of primary immunodeficiency diseases (PIDs) that are caused by congenital defects of the immune system. Today, over 100 inherited PIDs are known to exist, with an incidence estimate of 1 in 10,000 to 1 in 2000 among live births. These include X-linked agammaglobulinemia (Bruton's Disease), common variable immune deficiency (CVID), Chronic Granulomatous Disease (CGD), Familial Hemophagocytic Lymphohistiocytosis (FHL), and severe combined immune deficiency (SCID). PIDs result from defects in T-, B-, NK-, phagocytic cells or the complement system. If untreated, PIDs may associate with frequent life-threatening infections and debilitating illnesses. The genes responsible for most of these diseases have been identified due to modern advances in molecular diagnostics, which enabled early disease detection and adequate treatment. Mutation detection approaches are available to identify mutations through genotyping and direct sequencing. As would be expected, the incidence of these disorders in Saudi Arabia is higher than the world overall rates due to high consanguinity, and there is a need to delineate the molecular bases underlying them. The mission of the hereditary immunology unit is to investigate the underlying molecular defects responsible for the different PIDs in Saudi Arabia. We have so far succeeded in delineating many molecular defects for these disorders including SCID, CGD, and FHL.

Head of Unit:

Dr. Osama Alsmadi, PhD

Members:

Fadi Alkayal

Haya Al-Saud

Seham Al-Shehri

RESEARCH PROJECTS

Project Title: Underlying Molecular Genetic Defects of Severe Combined Immunodeficiencies (SCID) in Saudi Arabia, PI, RAC#2060 012

Primary Investigators: Osama Alsmadi and Hamoud Al-Mousa
Co-Investigators: Abdulaziz Al-Ghoniaim, Hasan Al-Dhekry, Hassan Al-Rayes, Saleh Al-Muhsen, and Rand Arnaout

PROJECT DESCRIPTION

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 including RAG1, RAG2, DCLRE1C (Artemis), NP, ADA, JAK3, IL2Rcg, etc. Families of patient's negative for mutations of the known SCID-causing 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 the underlying novel genetic defects. It is expected that data resulting from this study will benefit future counseling and newborn screening programs.

PROGRESS

Up to date, more than 100 families with SCID disease have been studied. Mutations in RAG1, RAG2, DCLRE1C, NP, Jak3 and ADA genes have been identified; some were novel in addition to the reported common mutations. Some cases so far had no identified mutations in the known disease causing genes and will be candidate for homozygosity mapping and whole genome linkage analysis. Five approved abstracts based on this work were presented in the last 2008 ESID International conference in Holland.

MAJOR FINDINGS

- Novel as well as common mutations were identified and essentially all from the AR type. No X-linked cases were identified.
- Hereditary Immunology Program is beneficial to the patients and their families in terms of molecular diagnosis, treatment, PGD, carrier testing and premarital and genetic counseling.
- Results present a foundation for the PID database.
- Result are summarized in the following table:

TOTAL	GENOTYPED?	SEQUENCED?
368 subjects (120 patients)	ALL	48 positive patients
SCID-CAUSING Genes Covered:	RAG1, RAG2, DCLRE1C(Artemis), ADA, ZAP70, IL7RJAK3, SH2D1, CD40, FOXP3, ILR2Cgama, NP	
RAG 242 (89P;19+)	DCLRe1c 242 (89P;10+)	ADA 38 (16P;7+)
RAG1 Ex6-Ex7 R975W (n=1)	ART Ex14-1 Insertion K428N (n=1)	ADA Ex4 K80R (n=2)
RAG1 EX3 R396H (n=2)	ART Ex6 G153R (n=1)	ADA Ex10 del nt 955-59 (n=1)
RAG1 Ex3 R394W Novel (n=1)	ART INSERTION EX13 TO EX14-2 (n=1)	ADA Ex7 G216R (n=1)
RAG1 EX3 S401P (n=2)	DELETION EX1, EX2, EX3 TO EX14-2 (n=1)	ADA Ex9 R282Q Novel (n=3)
RAG1 EX3 V433M (n=2)	ZAP70 20(8P;3+)	

RAG1 Ex4 R559S (n=1)	ZAP70 Ex12 G536S (n=2)	JAK3 41(16P;7+)
RAG1 EX5 R624H (n=1)	ZAP70 EX5 R190T Novel (n=1)	JAK3 Ex 7-8 Q305X Novel (n=6)
RAG2 Ex1 V81 Novel (n=1)		
RAG2 Ex1 insertion 211ins13 (n=1)	IL7R 12 (5P;0+)	JAK3 Ex 7-8 1012 delG (n=1)
RAG2 Ex1 Q4X Novel (n=1)		
RAG2 Ex1 R229P (n=1)	CD40 4(1P;1+)	NP 15(6P;3+)
RAG2 Ex1 R27Stop Novel (n=1)	CD40 Ex3 splice 151 gt>gc (n=1)	PNP Ex5 S163P Novel (n=3)
RAG2 Ex2 I444M Novel (n=1)		PNP Ex2 Splice site 47 G>C Novel (n=1)

Project Title: Underlying molecular defects of chronic granulomatous disease in a cohort of Saudi patients, PI, RAC# 2070 017.

Primary Investigators: Osama Alsmadi and Saleh Al-Muhsen

Co-Investigators: Abdulaziz Al-Ghoniaum, Hamoud Al-Mousa, Hasan Al-Dhekry, Rand Arnaout and Bandar Al-Saud

PROJECT DESCRIPTION

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

gP91^{phox}. Three other forms caused by AR defect in the other components of the NADPH oxidase system, encoding P22^{phox}, P47^{phox}, and P67^{phox} respectively. 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 Center. 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.

PROGRESS

- So far 55 patients with CGD were investigated. Novel and common mutations were identified.
- 250K Affymetrix was performed on a selected subset of the mutation-free patients for the purpose of homozygosity mapping using CNAG 3.0 software.

BELOW IS A SUMMARY OF THE CGD MOLECULAR FINDINGS

TOTAL	55
GENOTYPED	All
SEQUENCED	41 (16 positive for mutation)
NCF1	
NCF1 Ex2 36GT del (n=2)	
NCF1 Ex2 C334T (n=2)	
NCF2	
NCF2 Ex6 Q192STOP (n=3)	
NCF2 Ex3 R77X (n=2)	
CY24A	
CY24A Ex4 Y72H (n=1)	
CY24A Ex5 Intron 5 GG>TT donor Splice site Novel (n=3)	
CY2BB	
CY2BB Ex10 L406X (n=2)	
CY2BB Ex5 R130X (n=1)	

MAJOR FINDINGS

- We have identified both AR and X-linked forms of CGD
- Negative cases promises s source for novel genes discovery

Behavioral Genetics

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

Head of Unit:

Dana Bakheet, PhD

Members:

Nada Al Tassan, PhD

Dania Khalil, BSc

Latifa Al Sharif, BSc

Jameela Shinwari, MSc

RESEARCH PROJECTS/ACTIVITIES

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 the study is to identify families with the rare recessive disorders AOA types I and II, and screen for mutations in the common known genes APTX and SETX.

PROGRESS

Five families with AOA type I (family B,C,D) or II (family A and D) were enrolled in the study (2 or more affected individuals). Comprehensive screening for the whole open reading frame (ORF) of the related genes was performed and completed in all families. A novel truncating mutation (c.6859 C>T, R2287X) in exon 20 of the SETX gene was identified as the disease causing mutation in family A. The other four families with clear diagnosis have been negative for mutations in these genes indicating the genetics diversity of this disorder. Linkage analysis in one of these families Family D (3 affected) was performed using (10K micro-array chip) and a candidate region (LOD score of 3.2) harboring MRE11 gene which is implicated in AT-Like disorder was identified, sequence analysis revealed a common reported mutation W210C in exon 7 in all affected members of family D and the affected individuals from family C. A new locus have been identified in Family E (AOA2, four affected) and analysis of this locus in ongoing.

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 the study is to identify families with WMS which is a rare connective tissue disorder associated

with lens abnormalities, and screen for mutations in the common known genes (ADAMTS-10, FBN-1).

PROGRESS

Sequencing of the whole coding region of the related genes (ADAMTS-10, FBN1) is being performed in affected individuals from 5 families with WMS phenotype. A novel missense mutation in exon 13 of ADAMTS10 (c.1553 G>A) G518D was identified in one family. No pathogenic mutation was identified in the remaining 4 families. Linkage analysis on one family with 4 affected individuals revealed a disease locus in a 2.05-Mb region on 15q26.3, sequence of candidate genes is ongoing.

Project Title: Genetic evaluation of congenital eyelid and eye movement abnormalities. (2080020)

Investigators: Khan A, Al-Tassan N.

PROJECT DESCRIPTION

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

PROGRESS

Comprehensive screening for the whole open reading frame (ORF) of KIF21a was performed and completed in affected individuals and in two families with the dominant congenital fibrosis of the extraocular muscles type I (CFEOM1) phenotype. The common R954W missense mutation was identified in these families. Seventeen other patients have been enrolled in the study and mutational screenings have revealed several novel and reported polymorphisms in some of these genes and novel ROBO3 missense mutation

P771L was identified in a patient with synergistic convergence. Thirteen families (2 or more affected) with are being analyzed using 10-250K micro-array chips to identify possible new disease causing loci.

Project Title: Characterizing Genetic Abnormalities in Autistic Spectrum Disorder (ASD) patients in Saudi Arabia. (2080020)

Investigators: Al-Tassan N, Aldosari M, Nester M, Bakheet D.

PROJECT DESCRIPTION

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

PROGRESS

Seven families enrolled so far, Linkage analysis have revealed candidate loci on chromosome 7 in one family, sequencing of genes in this region is undergoing.

Project Title: Genetic Characterization of Hemoglobinopathies in Saudi Arabia (2080012).

Investigators: Bakheet D, Al Jafreer A, Warsy A, Al Anzi M, Al Tassan N

PROJECT DESCRIPTION

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

PROGRESS

Seventy β - thalassaemia patients were enrolled from KKHU and KFSSHRC. Screening of the β - globin gene identified a number of novel and reported variants and mutations.

Project Title: Identification of Sulfonylurea Receptor SUR1 and Potassium Inward Rectifying Receptor Kir6.2 Genes mutations in Saudi Patients With Persistent Hyperinsulinemic Hypoglycemia of Infancy (Nesidioblastosis). (2020 007).

Investigators: Bakheet D, Tassan N and Bin Abbas Bassam

PROJECT DESCRIPTION

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

PROGRESS

15 patients were enrolled from KKSH&RC Screening for both genes identified a number of novel and reported variants.

FUTURE RESEARCH DIRECTION

The main future goal is to establish a molecular research facility that utilizes the latest molecular analysis techniques to study genetically diverse complex disorders to identify new disease causing genes and novel mutations and to study the functional role of these mutations.

PUBLICATIONS AND POSTERS

- ↪ Khan, AO, Khalil, DS, and Al-Tassan, NA, Congenital fibrosis of the extraocular muscles type I (CFEOM1) on the Arabian Peninsula. *Ophthalmic Genet*, 2008; 29(1): 25-8.
- ↪ Khan, AO, Oystreck, DT, Al-Tassan, N, Al-Sharif, L, and Bosley, TM, Bilateral synergistic convergence associated with homozygous ROB03 mutation (p.Pro771Leu). *Ophthalmology*, 2008; 115(12): 2262-5.
- ↪ Bohlega S, Al Sharif L, AlKhairallah B, Al Mubarak D, Bakheet D and Al Tassan N. Molecular analysis of APTX and SETX genes in families with ataxia with oculomotor apraxia in Saudi Arabia (2008). *Journal of Neurology* 255 (S2):69-70. (Poster)

- ↪ Bakheet, D, Al Tassan N, Al Sharif I, Khalil D, Khairallah T, Bohlega S. Molecular Characterization of Ataxia Oculomotor Apraxia in Saudi Arabia. 58th annual meeting of the American Society of Human Genetics,, Philadelphia, USA, 11-15 November 2008.

Sequencing Core Facility

The main objective of the section is the sequencing and genotyping activities within the Research Centre. The laboratory uses state-of-the-art technology and methodology to generate high quality DNA sequences. The Core provides services, which can be used for sequence analysis of plasmid, PCR and large DNA samples. The Unit is involved in a broad range of medical scientific and diagnostic work, contributing to most of the research projects carried out in the Department of Genetics. By introducing ABI 3730xl DNA Sequencer and the implementation of a new purification SPRI system we have improved and increased the throughput of the Core to generate sequencing data up to 12 x 96-well plates (~1200 samples) a day. We also help and advise in the troubleshooting of sequencing and genotyping problems. Currently, the Core cooperates with 80 researches within the Research Centre and also from outside e.g. the King Saud University. This year we have generated approximately 10,000 genotyping results and 150,000 sequencing reads.

Head of Unit:

Dorota Monies, PhD

Members:

Mohamed Rajab, BSc

Shamsa Al-Enazi, BSc

RESEARCH PROJECTS/ACTIVITIES

Project Title: Molecular Genetic Characterization of Hereditary Gastrointestinal Diseases (2080016).

Investigators: Rahbeeni Z, Monies D, Al-Zaidan H, Mehadib A, Al-Edreesi M, Faqih M, Meyer B

PROJECT DESCRIPTION

The objective of the study is to identify families with the rare recessive gastrointestinal disorders such as MVID or CTE, and screen for mutations of known (Myo5B, EpCAM) and novel candidate genes.

PROGRESS

Three families with MVID (family: 1,2,3) and two with CTE (family 4 and 5) were enrolled in the study (7 affected individuals). Comprehensive screening of the related genes was performed and completed in all families. Direct sequencing of all 40 exons of MYO5B revealed novel homoallelic nonsense mutations in exon 24 and exon 36 (Q1047X, E1589X) in the affected members of the family 1 and family 3, respectively. In two CTE families, 1 bp insertion (C) was detected in exon 5 of EpCAM, causing the protein truncation in exon 6. Sequencing of the related genes in the family 2 is ongoing.

THE DEPARTMENT OF HUMAN
CANCER GENOMIC RESEARCH

The Department of Human Cancer Genomic Research

The mission of the Department of Human Cancer Genomic Research (DHCGR) is to conduct translational research on cancers that are more prevalent in the Kingdom of Saudi Arabia. The main focus of the Research Center 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 2008 has been another eventful year scientifically during which we were able to publish 15 full length articles in reputable peer-reviewed scientific journals. In addition, for the first time in the history of this prestigious institution, seventeen (17) abstracts were accepted for the 2009 annual meeting of the American Association of Cancer Research that will be held in Denver, Colorado in April. This was indeed, a major accomplishment because besides USA, Japan and South Korea, no other country in the world had more abstracts accepted in the AACR meeting than the DHCGR. All this was accomplished because of the dedication of the staff of DHCGR, aimed towards the goals of the department to improve the overall survival of cancer patients in Saudi Arabia. Integration of three major components of our laboratory studies, (i) clinical research using tissue microarray as well as patient's clinical history, (ii) *in-vitro* studies using cell lines to study the functional aspects of these cancers and finally correlating these findings (iii) *in-vivo* using either SCID or Nude mice has greatly improved our chances in better understanding the underlying patho-physiology of cancer. This combined approach has definitely enhanced and improved the chances of treating these cancers using targeted therapy against certain genes that are being discovered with the help of these techniques.

We hope to continue with our research activities in the same fervor and enthusiasm to make 2009, even more productive than last year.

Chairman:

Khawla S. Al-Kuraya , MD, FCAP

Scientific Staff:

Jehad Abubaker, PhD

Hassan Al-Dosari

Saeeda Omar Ahmed, BSc

Maqbool Ahmed, PhD

Valerie Atizado, BSc

Valorie Balde

Prashant Bavi MD

Wael Haqawi, BSc

Azhar R Hussain, MBBS

Zeenath Jehan, PhD

Shahab Uddin Khan, PhD

Azadali Moorji BSc

Maha Al Rasheed BSc

Abdul Khalid Siraj MSc

Devarajan Sriraman B.Com, MCA

Meher Sultana, MSc

Administrative Support Staff:

Saad Al Odaib

Maria Victoria Concepcion

Selah Fulgencio

Myra Maningas

The Department of Human Cancer Genomic Research is further divided into 3 closely inter-related sections.

- Section of Experimental Pathology
- Section of Molecular Oncology
- Biological Repository Center

SECTION OF EXPERIMENTAL PATHOLOGY

During the year 2008, the section of Experimental Pathology has been able to identify different genetic targets can be utilized as either diagnostic markers or as therapeutic targets. We were able to identify FASN as a novel therapeutic target for the treatment of colo-rectal carcinoma. In addition, we were also able to detect cross-talk between different survival pathways in DLBCL. These findings were important to better understand the underlying patho-physiology of DLBCL from this region. 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 tumor and normal tissue samples. DNA and RNA extracted from these frozen samples are being utilized for mutational analysis and differential expression studies in various projects.

TASKS

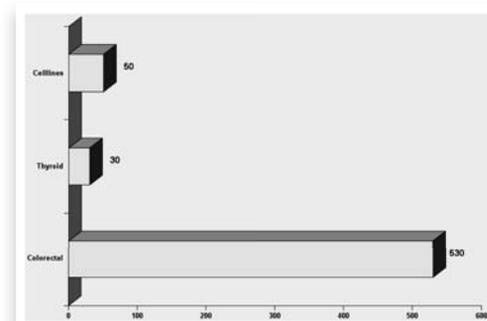
Collect and maintain archives of frozen tissues (normal and neoplastic), serum, paraffin blocks and commercial cell lines.

ACTIVITIES

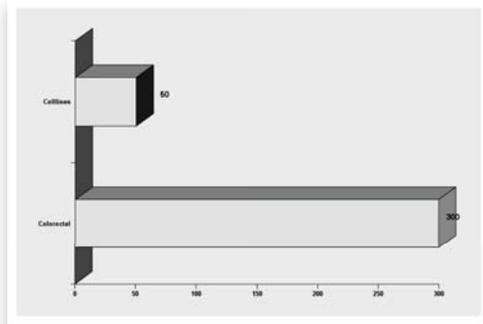
BRC is handling a number of different projects in which biological samples are being optimally stored and further processing is being done as and when requested by the researchers.

1. Processing biomaterial (DNA and/or RNA extraction from blood, frozen tissues and paraffin blocks) for various research projects – a total of 960 specimens were processed in the year 2008.

DNA Extraction from Blood, Fresh frozen tissues and Paraffin Blocks



RNA extraction from Blood, Fresh frozen tissues and Paraffin Blocks



2. Cell blocks prepared from cell lines used for immunohistochemistry -25.
3. Commercial cell lines acquired from ATCC and other biorepository centers expanded and grown in bulk over 2000 vials frozen and stored in liquid nitrogen.
4. Processing of fresh tissue for frozen sections and formalin fixed paraffin embedded (FFPE) tissues from archival paraffin blocks for routine H&E staining and immunohistochemistry. This may include fixation, paraffin embedding, tissue cutting and section staining. Sections are cut and stained for all routine histochemical staining including hematoxylin and eosin.

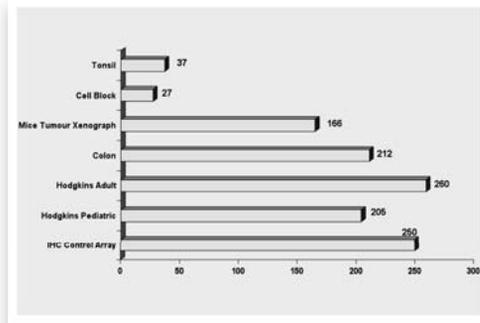
Number of samples processed	
Paraffin blocks	4150
H & E stain	4150
Immunohistochemistry	2205
Frozen section	500

5. Storing biomaterial under controlled temperature:
 - ∞ Storage of various commercial cell lines which are being used for various ongoing research projects in our department
 - ∞ Maintaining supply of liquid nitrogen for cryomed freezers for department of genetics, Research Centre
 - ∞ Storage of tissues for project # 2060-007.

6. 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 established TMA technology and has an extensive archival of tumor specimens in a TMA format. A total of 1157 tumor and normal tissue specimens were arrayed in a TMA format in year 2008. In addition we have a cell line block TMA.



RESEARCH PROJECTS

There are five active RAC approved projects for the year 2008.

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

Investigators: Khawla S. Al-Kuraya, Shahab Uddin, Prashant P. Bavi, Maqbool Ahmed, Abdul K. Siraj, Jehad Abubaker, Azhar R. Hussain, Zeenath Jehan

Project Title: Inhibition of Fatty Acid Synthase Suppresses c-Met Kinase and Induces Apoptosis in Diffuse Large B Cell Lymphoma

PROJECT DESCRIPTION

Fatty acid synthase (FASN), the enzyme responsible for *de novo* synthesis of fatty acids has emerged as a potential therapeutic target for several cancers however its role in diffuse large B-cell lymphoma (DLBCL) has not been fully elucidated. In this study, we investigated the role of FASN in a large series of DLBCL tissues in a tissue micro array (TMA) format followed by *in vitro* studies using DLBCL cell lines. FASN was found to be expressed in 62.6% (162/259) DLBCL samples and was seen in highly proliferative tumors manifested by high Ki67 ($p < 0.0001$). Significant association was found between tumors expressing high FASN and c-Met tyrosine kinase ($p < 0.0002$) as well as p-AKT ($p = 0.0309$). *In vitro*, pharmacological FASN inhibition and siRNA targeted against FASN triggered caspase dependent apoptosis and suppressed expression of c-Met kinase in DLBCL cell lines which further highlighted the molecular link between FASN and c-Met kinase. Finally, simultaneous targeting of FASN and c-Met with specific chemical inhibitors induced a synergistically stimulated apoptotic response in DLBCL cell lines. These findings provide evidence that FASN via c-Met tyrosine kinase playing critical role in the carcinogenesis of DLBCL

and strongly suggest that targeting FASN may have therapeutic value in treatment of DLBCL.

PROGRESS

Manuscript submitted, 2009.

Project Title: X-Linked Inhibitor of Apoptosis Protein Expression is a Bad Prognostic Marker in DLBCL and is Regulated by Hepatocyte Growth Factor/c-Met Pathway via AKT Pathway.

PROJECT DESCRIPTION

The inhibitor of apoptosis protein (IAP) family members such as X-linked Inhibitor of Apoptosis Protein (XIAP) and Survivin are essential for cell survival and anti-apoptosis in lymphoma cells. It is also known that expression of XIAP is controlled by different survival pathways in various cancers, however, the relationship between the survival pathways and XIAP is not fully understood in diffuse large B-cell lymphoma (DLBCL). We therefore hypothesized that the hepatocyte growth factor (HGF) activation in DLBCL via c-Met receptor regulates IAP protein expression in DLBCL through AKT pathway. In this study, XIAP, activated AKT and c-Met expression was assessed using 301 Middle Eastern lymphoma samples using tissue microarray analysis. Furthermore the role of HGF/c-Met pathway through AKT and XIAP was investigated using c-Met inhibitor (PHA665752) and small interfering RNA (siRNA) targeted against c-Met in a panel of DLBCL cell lines. XIAP was found to be over-expressed in 55% of DLBCL cases and it showed significant correlation with c-Met protein over-expression (62.0 %, $p = 0.0002$). In addition, c-Met over-expression was significantly associated with activated AKT (80.7%, $p = 0.0274$). Furthermore, XIAP expressing tumors tend to have high proliferation rate as manifested by the high correlation between XIAP and Ki67 (65.8%, $p < 0.0001$). Interestingly, patients with high XIAP expression were found to have a bad survival ($p = 0.0421$). *In vitro* analysis showed that HGF stimulation of DLBCL cell lines activated c-Met and enhanced XIAP expression. Activation of XIAP expression by HGF was inhibited by

pharmacological inhibitors and siRNA targeting c-Met and AKT. In addition, PHA665752 treatment of DLBCL cell lines induced apoptosis in a dose dependent manner via activation of the intrinsic apoptotic pathway and down-regulation of XIAP. In summary, our data suggest that XIAP expression is a prognostic factor in DLBCL and that targeting c-Met *in vitro* could inhibit XIAP protein expression and induce apoptosis via AKT dependent mechanism. Therefore c-Met-AKT-XIAP relationship should be explored further as a potential therapeutic target in DLBCL.

PROGRESS

Manuscript in preparation.

Project Title: Curcumin Suppresses Constitutive Activation of NF κ B and Requires Functional Bax to Induce Apoptosis in Burkitt's Lymphoma Cell Lines.

PROJECT DESCRIPTION

We provide evidence that curcumin, a natural compound isolated from rhizomes of plant *Curcuma longa*, induces apoptosis in several Burkitt's lymphoma (BL) cell lines expressing Bax protein (AS283A, KK124 and Pa682PB), while it has no effects in cell lines with no Bax expression (BML895 and CA46). Our data demonstrate that curcumin-treatment results in down-regulation of constitutive activation of NF κ B via generation of reactive oxygen species where it causes conformational changes in Bax protein leading to loss of mitochondrial membrane potential and release of cytochrome c to the cytosol. This leads to activation of caspase-9, caspase-3, and polyadenosin-5'-diphosphate-ribose polymerase (PARP) cleavage leading to caspase-dependent apoptosis. In addition, curcumin treatment of BL cell lines also causes up-regulation of DR5; however this up-regulation does not result in apoptosis. Importantly, co-treatment with curcumin and TRAIL induces apoptosis in Bax deficient cell lines. Taken together, our findings suggest that curcumin is able to induce apoptosis in Bax positive cell lines, while combinations with TRAIL result in apoptosis in Bax negative cell lines. These findings also raise the

possibility that incorporation of curcumin in treatment regimens may provide a novel approach for the treatment of Burkitt's lymphomas and provide the molecular basis for such future translational efforts.

PROGRESS

Manuscript published in *Molecular Cancer Therapeutics* 2008, 7(10); 3318-29.

THYROID

Investigators: Khawla S. Al-Kuraya, Shahab Uddin, Abdul K. Siraj, Azhar R Hussain, Maqbool Ahmed, Prashant P. Bavi, Jehad Abubaker, Zeenath Jehan

Project Title: Inhibition of c-Met as Therapeutic Strategy for Papillary Thyroid Cancer.

PROJECT DESCRIPTION

The hepatocyte growth factor (HGF) receptor c-Met is a tyrosine kinase receptor with established oncogenic properties. We have previously shown that c-Met is usually overexpressed in Middle Eastern Papillary Thyroid Cancer (PTC) and it has strong prognostic significance. Yet the implication of c-Met inhibition in PTC need to be further elucidated. A panel of c-Met over-expressing PTC cell lines was used to examine the effect c-Met small molecular pharmacological inhibitor (PHA-665752) and small interfering RNA (siRNA) on cell viability, apoptosis and downstream signaling pathway. Our data showed that PHA-665752 treatment of PTC cell lines inhibited cell proliferation and induced apoptosis in a dose dependent manner in all cell lines studied. Additionally, PHA-665752 treatment caused dephosphorylation of c-Met, AKT and its downstream effector molecules FOXO1, GSK-3 and pBad. Furthermore, treatment of PTC cell lines with PHA-665752 resulted in activation of caspases-9 and 3, cleavage PARP and apoptosis. Finally, HGF, a ligand of c-Met, stimulated the growth of all PTC cell lines via activation of c-MET and AKT. In addition, pre-treatment of PTC cell line with PHA-665752 abrogated

the HGF stimulated growth and activation of c-met and AKT further suggesting the critical role of c-met and AKT pathway in PTC pathogenesis. Altogether these data indicate that targeting of c-Met using small molecular inhibitor is a novel therapeutic approach for the treatment of PTC.

PROGRESS

Manuscript in preparation.

Project Title: Enhanced Leptin Receptor Expression Identifies an Aggressive Subset of Middle Eastern Papillary Thyroid Cancer.

PROJECT DESCRIPTION

A number of studies published recently focused on putative role of leptin in the pathogenesis of various primary human malignancy. However, the role of leptin and leptin receptor (Ob-R) in papillary thyroid cancer has not yet evaluated current study was aimed first at investigating Ob-R protein expression, and its clinicopathological correlation in large cohort of Middle Eastern PTC. Then we investigate the effect of leptin on proliferation and apoptosis of PTC cells and the early signaling events involved. Ob-R immunostaining was detected in (57.4%) PTCs tumors that overexpressed Ob-R tend to present with nodal metasis, extrathyroid extension and all cell variant histologic subtype. *In vitro* analysis showed that leptin stimulated cell proliferation and inhibit apoptosis via activation of phosphatidylinositol 3' kinase (PI3K)/AKT signaling pathway. The proliferation and anti-apoptotic effects of leptin were abolished by inhibition of Ob-R with small interference RNA (siRNA) and PI3K/AKT with LY294002. Finally, our data showed that Ob-R is commonly expressed in Middle Eastern PTC and leptin stimulates proliferation inhibits apoptosis in human PTC via PI3K/AKT pathway activation. These effects of leptin provide a link between obesity and PTC and may represent a target for anti cancer drug development.

PROGRESS

Manuscript in preparation.

Project Title: Methylation Status of Target of Methylation Associated Silencing (TMS1) Gene Predicts Outcome in Middle Eastern Papillary Thyroid Cancer Patient.

PROJECT DESCRIPTION

Gene silencing associated with aberrant methylation of promoter region CpG islands is an acquired epigenetic alteration that can inactivate tumor suppressors and other genes in several human cancer. However the role of aberrant tumor suppressor gene methylation in predicting the outcome of papillary thyroid cancer (PTC) remains unsatisfactory. We examined the methylation status of 24 candidate tumor suppressor genes in 50 PTC and 3 PTC cell lines by conventional methylation specific PCR. Seven genes demonstrated a relatively high frequency of aberrant methylation: RAS1 (94%), HIC1 (55%), GSTP1 (31%), P14 (25%), TMS1 (21%), DCR1 (19%) and SERP (12%). Six genes (BRCA1, P16^{INK4A}, P15^{INK4B}, MGMT, BLU and APC) showed a low frequency (2-6%) of methylation, and no methylation was detected for the remaining eleven genes (APAF1, FANCE, FAS, MINT25, P73, MLH1, DAPK, RARB, CASP8, E-Cadherin and SOX1). *In vivo*, methylation status of target of methylation associated silencing (TMS1) was associated with protein level of TMS1. (P=XX), significantly higher in male PTC (XX) and more interestingly significant association with poor patient survival. Multivariate analysis revealed that TMS1 hypermethylation is independent factor for predicting poor survival in patient with PTC. (95% confidence interval, CI). Furthermore, *in vitro* analysis showed that TMS1 transcripts were not observed or present at low levels in PTC cell lines were restored by treatment with demethylating agent 5-aza-2'deoxyctidine (5-Aza-dC). So TMS1 methylation may be a promising molecular marker to predict patient outcome in Middle Eastern PTC, and may be used as therapeutic demethylating target.

PROGRESS

Manuscript in preparation.

COLON

Investigators: Khawla S. Al-Kuraya, Shahab Uddin, Jehad Abubaker, Prashant P. Bavi, Zeenath Jehan, Azhar R. Hussain, Maqbool Ahmed

Project Title: c-Met Inhibitor Sensitizes Human Colorectal Cancer Cells to TRAIL-Induced Apoptosis.

PROJECT DESCRIPTION

Colorectal cancer (CRC) is still carrying a high morbidity and mortality despite improvement in treatment strategies. More recently, advances in the understanding of tumor biology have led to the development of targeted therapies allowing progress in the treatment of colorectal cancer. One attractive target that is gaining attention is the hepatocyte growth factor (HGF) and its receptor c-MET. To better understand the role of c-Met signaling and its association with other survival molecules in CRC, we investigated the role of c-Met in a large series (400) of Middle Eastern CRC patient samples. Using immunohistochemistry on a TMA format, we evaluated the expression of c-Met and its association with p-AKT, XIAP and Ki67 and found that c-Met was over-expressed in 347/400 cases of CRC (86.8%) and was strongly associated with expression of p-AKT (91.1%, $p < 0.01$), XIAP (92%, $p < 0.01$) and Ki67 (89%, $p < 0.01$). As HGF/c-Met has also been shown to upregulate the expression of death receptor 5 (DR5), we next examined the effect of PHA665752, a selective c-Met tyrosine kinase inhibitor either alone or in combination with TNF-related apoptosis inducing ligand (TRAIL) on a panel of CRC cell lines and found that 48 hours PHA665752 treatment of CRC cell lines inhibited cell growth and induced apoptosis in a dose dependent manner in all cell lines. Additionally, PHA665752 treatment caused dephosphorylation of c-Met, AKT and its downstream effector targets FOXO1, GSK-3 and pBad and eventually apoptosis via the intrinsic apoptotic pathway. PHA665752 treatment also caused down-regulation of inhibitor of apoptosis proteins, XIAP, cIAP-1 and -2 and Survivin. Finally, treatment of CRC cell lines with

TRAIL in combination with PHA665752 significantly synergized the cells to undergo apoptosis via activation of the extrinsic apoptotic pathway as compared to treatment with PHA665752 and TRAIL alone. In summary, data presented here demonstrate a significant correlation between the expression of c-Met, active AKT and XIAP in CRC patients. This data also indicates that inhibition of c-Met signaling by PHA665752 in combination with TRAIL significantly inhibits cell growth and induces apoptosis in CRC cell lines. This may have significant clinical implications as a therapeutic target in the treatment of CRC.

PROGRESS

Manuscript in preparation.

Project Title: KRAS Alteration in the Middle Eastern CRC and Its Clinicopathological Significance.

PROJECT DESCRIPTION

MAPK pathway regulates cell proliferation, differentiation, senescence and apoptosis. The first gene in MAPK kinase pathway is RAS gene, which is reported to be mutated in most human cancers. KRAS is the main gene of RAS family to be mutated in CRC. KRAS encodes for two splice variants, KRAS-2A and 2B, and KRAS activating mutations affect both isoforms. Our aim was to study the incidence of KRAS splice variants, KRAS mutation and their relationships with various clinicopathological characteristics in Middle Eastern colorectal cancer (CRC). In this study, over 300 CRC cases were analyzed for KRAS mutation (codon 12, and 13) by direct PCR sequencing. Immunohistochemistry was used to study the protein expression of KRAS-2A and 2B isoforms. KRAS gene mutations were seen in 80/285 CRC (28.1%) and of the mutated cases majority of the mutations were seen in codon 12 (81.2%) as compared to codon 13 (18.8%). CRC with KRAS mutations were associated with a poor overall survival ($P = 0.0009$), which remained significant in a multivariate analysis with age, gender, stage, differentiation and MSI status. Further, KRAS mutations at codon 12 were associated with a poor overall survival of 64.4% at

5 years as compared to a 5 year overall survival of 75.8% and 78.2% with codon 13 mutation and absence of K-ras mutations respectively ($P = 0.0234$). KRAS-2A protein expression was predominantly seen in the cytoplasm, while KRAS-2b protein was nucleus. KRAS-2A over-expression was significantly associated with right colon, adenocarcinoma, and p27kip1. Interestingly, KRAS-2A over-expression was associated with better overall survival ($P = 0.0437$), which remained significant in a multivariate analysis. On the other hand, KRAS-2B over-expression (32.2%) was significantly associated with larger tumor size ($P = 0.023$), and inversely correlated with p27kip1 protein. In concordance with earlier reports KRAS mutation was an independent prognostic marker for poor survival and presence of codon 12 mutation was associated with a poor outcome. Our results highlight the differential role of KRAS isoforms in CRC and underline the importance of KRAS alterations as a potential therapeutic target for Middle Eastern CRC.

PROGRESS

Manuscript in preparation.

Project Title: Prognostic Value of Ubiquitin-Conjugating Enzyme E2C Expression in Middle Eastern CRC.

PROJECT DESCRIPTION

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 preparation.

OVARY

Investigators: Khawla S. Al-Kuraya, Shahab Uddin, Maqbool Ahmed, Jehad Abubaker, Abdul Khalid Siraj, Prashant P. Bavi, Zeenath Jehan, Azhar R. Hussain

Project Title: Bortezomib Induces Apoptosis Via SKP2 Down Regulation and Synergizes With Cisplatin in the Killing of Ovarian Cancer Cells.

PROJECT DESCRIPTION

The ubiquitin-proteasome system (UPS) mediates targeted protein degradation. Notably, the UPS determines levels of a key checkpoints proteins controlling apoptosis and proliferation by controlling protein half life. SKP2,

an F-box protein which is known to be overexpressed in variety of cancer is regulated via UPS. In this study, we first investigated the role of SKP2 and its ubiquitin-proteasome pathway in epithelial ovarian cancer (EOC) using a panel of cell lines, 156 EOC tumor samples and NUDE mouse model. SKP2 protein expression was detected by Immunohistochemistry in 130 epithelial ovarian cancer (EOC) using tissue microarray analysis. Twenty of 130 (13.2%) EOCs had SKP2 overexpression which was significantly associated with low p27KIP1 protein level. EOC subset with high SKP2 and low p27KIP1 showed high proliferation rate manifested by high expression of Ki67 ($P < 0.0014$). We show that induction of EOC apoptosis by proteasome inhibitor Bortezomib is involved mitochondrial pathway and activation of caspases. In addition, Bortezomib induced apoptosis is accompanied by down regulation of SKP2 and accumulation of p27KIP1. Furthermore, combination of Bortezomib and cisplatin (which is commonly used in treatment of EOC) led to synergistic killing of EOC cells, with calculated combination indexes well below 1.0. Finally, treatment with proteasome inhibitor (Bortezomib) slows the growth of MDAH2774 ovarian carcinoma xenograft in nude mice via down regulation of SKP2 and accumulation of p27. Taken together, these results delineate a novel mechanism of EOC killing by Bortezomib that involves down regulation of SKP2. Moreover, our findings suggest that the combination of Bortezomib plus cisplatin may have therapeutic value in treatment of EOC.

PROGRESS

Manuscript submitted to Molecular cancer therapeutics.

Project Title: Prevalence of COX2 Expression in Middle Eastern CRC and the Effect of COX2 Inhibitors on Cell growth in the Mouse Model of CRC.

PROJECT DESCRIPTION

Overexpression cyclooxygenase-2 (COX2) has been shown to play a major role in colorectal cancer (CRC) pathogenesis. However the role and prevalence

of COX2 has not been explored in the Middle Eastern CRC. Current study was aimed first at investigating COX2 protein, and its clinicopathological correlation in >400 Middle Eastern CRC using tissue microarray analyses. Then we investigate the effect of pharmacological COX2 inhibitor (NS398) and small interfering RNA (siRNA) on cell viability apoptosis and its down stream signaling pathway on a panel of CRC cell lines and in nude mice xenograft model. COX2 immunostaining was detected in 53.8% (211/392) of the CRC tested. COX2 overexpression is seen more frequently in mucinous histological subtype, poorly differentiated tumors and tumor with lymph node metastasis (p value 0.0089; $p=0.0004$ and $p= 0.198$ respectively). CRC with high COX2 expression have a high proliferative index (Ki67; $p= 0.0293$). *In vitro* analysis showed that pharmacological COX2 inhibitor NS398, aspirin and gene silencing by COX2 specific siRNA triggers apoptosis via impairment of AKT phosphorylation and inactivation of PI3K/AKT signaling pathway. Finally, treatment of CRC HT-29 cell line xenograft with NS398 Inhibitor resulted in growth inhibition of tumors in nude mice via down regulation of COX2 and AKT activity.

So in summary our data showed the COX2 play an important pathological role in malignant transformation and progression of Middle Eastern CRC and identify COX2 as a potential biomarker and novel therapeutic target in distinct molecular subtypes of CRC.

PROGRESS

Manuscript in revision, International Journal of Cancer.

Project Title: PIK3CA Alterations in Middle Eastern Ovarian Cancers and its Clinicopathological Significance.

PROJECT DESCRIPTION

PI3K/AKT signaling pathway plays an important role in cell growth, proliferation, and tumorigenesis of various malignancies. This signaling pathway has been shown to be frequently altered in several human

cancers including ovarian cancers. However the role of this oncogenic signaling pathway has not been explored in the Middle Eastern epithelial ovarian cancer (EOC). Therefore, we investigated PI3K/AKT genetic alterations such as PIK3CA amplification, PIK3CA mutation, PTEN protein loss and their relationships with various clinicopathological characteristics in 156 EOCs. Fluorescence *in situ* hybridization (FISH) technique and DNA sequencing were used to analyze PIK3CA amplification and mutation respectively. Expression of PIK3CA protein expression (p110 α), PTEN, p-AKT and Ki-67 was analyzed by immunohistochemistry. PIK3CA amplification was seen in 54 of 152 (35.5%) EOC cases analyzed; PIK3CA gene mutations in 6/153 EOC (3.9%); KRAS mutations in 3/154 EOC (1.9%), BRAF mutations in 3/156 EOC (1.9%), p53 mutation in 50/154 EOC (32.5%), and loss of PTEN protein expression in 33/144 EOC (22.9%). p110 α overexpression was associated with increased phosphorylation of AKT-Ser 473 and with the proliferation marker Ki-67. Our data showed mutual exclusivity between the molecular event of PIK3CA amplification and mutations in PIK3CA, KRAS, BRAF genes, which suggests that each of these alterations may individually be sufficient to drive ovarian tumor pathogenesis independently. High prevalence of genetic alterations in PI3K/AKT pathway in a Middle Eastern ovarian carcinoma provides genetic evidence supporting the notion that dysregulated PI3K/AKT pathways play an important role in the pathogenesis of ovarian cancers.

PROGRESS

Submitted to *Modern Pathology*.

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

has already started giving dividends as many as 15 full length manuscripts were published from the DHCGR in the year 2008. 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.

PUBLICATIONS

- ↪ Uddin S, Khan AS, Al-Kuraya K. Developing curcumin into a viable therapeutic for lymphoma. *Expert Opin Investig Drugs*. 2009;18:57-67.
- ↪ Siraj AK, Ibrahim M, Al-Rasheed M, Rong B, Al-Dayel F, Uddin S, Al-Kuraya K. RAD52 polymorphisms contribute to the development of papillary thyroid cancer susceptibility in Middle Eastern population. *J Endocrinol Invest*. 2008;31:893-9.
- ↪ Uddin S, Hussain AR, Ahmed M, Belgaumi A, El-Solh H, Ezzat A, Al-Dayel F, Bavi P, Al-Kuraya K. S-phase kinase protein 2 is an attractive therapeutic target in a subset of diffuse large B cell lymphoma. *J Pathol*. 2008;216:483-494.
- ↪ Uddin S, Siraj AK, Al-Rasheed M, Ahmed M, Bu R, Myers J, AlNuaim A, Al-Sobhi S, Al-Dayel F, Bavi P, Hussain AR, Al-Kuraya K. Fatty Acid Synthase and AKT pathway signaling in a subset of papillary thyroid cancers. *J Clin Endocrinol Metab*. 2008;93:4088-97.
- ↪ Hussain AR, Maqbool A, Al-Jomah N, Khan A, Manogaran P, Sultana M, Abubaker J, Plataniias L, Al-Kuraya K, Uddin S. Curcumin suppresses constitutive activation of NFkB and requires functional Bax to induce apoptosis in Burkitt's lymphoma cell lines. *Molecular Cancer Therapeutics*. 2008;7:3318-29.
- ↪ Jehan Z, Siraj AK, Abubaker J, Ruiz C, Simon R, Sultana M, Uddin S, Bavi P, Hussain A, Razack S, Ezzat A, Al-Dayel F, Sauter G, Al-Kuraya KS. Distinct Gene Expression Profiles: Nodal versus Extranodal Diffuse Large B-Cell Lymphoma. *Oncology*. 2008; 75:71-80.
- ↪ Siraj AK, Ibrahim M, Al-Rasheed M, Abubaker J, Bu R,

- Siddiqui SU, Al-Dayel F, Al-Sanea O, Al-Nuaim A, Uddin S, Al-Kuraya KS. Polymorphisms of selected Xenobiotic Genes contribute to the development of Papillary Thyroid Cancer susceptibility in Middle Eastern population. *BMC Med Genet*. 2008;9:61.
- ↔ Holst F, Stahl P, Hellwinkel O, Dancu AM, Krohn A, Wuth L, Heupel C, Lebeau A, Terracciano L, Al-Kuraya K, Jänicke F, Sauter G, Simon R. Reply to "ESR1 gene amplification in breast cancer: a common phenomenon?" *Nat Genet*. 2008;40:810-812.
 - ↔ Trujillo C, Lebel RR, Al-Kuraya KS, Al-Sanea N. Colorectal carcinomas from Middle East. Molecular and tissue microarray analysis of genomic instability pathways. *Saudi Med J*. 2008;29:925-8.
 - ↔ Uddin S, Ahmed M, Bavi P, El-Sayed R, Al-Sanea N, Abduljabbar A, Ashari L, Samar Alhomoud S, Al-Dayel F, Hussain A, Al-Kuraya K. Bortezomib (Velcade®) Induces p27Kip1 Expression through SKP2 degradation in colorectal cancer. *Cancer Research*. 2008;68:3379-88.
 - ↔ Abubaker J, Bavi P, Al-Harbi S, Ibrahim M, Siraj AK, Al-Sanea N, Abduljabbar A, Ashari LH, Alhomoud S, Al-Dayel F, Uddin S, Al-Kuraya KS. Clinicopathological analysis of colorectal cancers with PIK3CA mutations in Middle Eastern population. *Oncogene*. 2008;27:3539-45.
 - ↔ Al-Dayel F, Al-Rasheed M, Ibrahim M, Bu R, Bavi P, Abubaker J, Al-Jomah N, Mohamed G, Moorji A, Uddin S, Siraj A, Al-Kuraya K. 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. *Leukemia and Lymphoma*. 2008;49:122-9.
 - ↔ Bavi P, Abubaker J, Hussain A, Sultana M, Al-Dayel F, Uddin S, Al-Kuraya K. Reduced or absent Cyclin H Expression Is An Independent Prognostic Marker For Poor Outcome In Diffuse Large B Cell Lymphoma. *Human Pathology*. 2008 39:885-94.
 - ↔ Bavi PP, Abubaker JA, Jehan ZD, Al-Jomah NA, Siraj AK, Al-Harbi SR, Atizado VL, Abduljabbar AS, Alhomoud SJ, Ashari LH, Al-Dayel FH, Uddin S, Al-Kuraya KS, Alsanee NA. Colorectal carcinomas from Middle East. Molecular and tissue microarray analysis of genomic instability pathways. *Saudi Med J*. 2008;29:75-80.
 - ↔ Abubaker J, Jehan Z, Bavi P, Sultana M, Al-Harbi S, Ibrahim M, Al-Nuaim A, Ahmed M, Amin T, Al-Fehaily M, Al-Sanea O, Al-Dayel F, Uddin S, Al-Kuraya K. Clinicopathological analysis of papillary thyroid cancer with PIK3CA alterations in a Middle Eastern population. *J Clin Endocrinol Metab*. 2008;93:611-618.

ABSTRACTS ACCEPTED AND PRESENTED

- Uddin S, Hussain AR, Bavi P, Al-Kuraya K. Fatty Acid Synthase and Diffuse Large B-cell Lymphoma. 50th ASH Annual Meeting, December 6-9, 2008, San Francisco, California.
- Al-Kuraya K. Fatty acid synthase is a potential therapeutic target in Micro-satellite-unstable colorectal cancers. 20th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, October 21-24, 2008, Geneva, Switzerland.
- Jehan Z, Bavi P, Hussain A, Alsbeih G, Al-Sanea N, Abduljabbar A, Ashari L, Alhomoud S, Al-Dayel F, Uddin S, Al-Kuraya K. PIK3CA amplification is an independent predictor of better survival in colon cancer patients of Middle East. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
- Jehan Z, Abubaker J, Bavi P, Uddin S, Al-Kuraya K. Genetic alterations of PIK3CA in Liver cancer of Saudi Arabia. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
- Hussain A, Ahmed M, Bavi P, Al-Sanea N, Abduljabbar A, Ashari L, Alhomoud S, Al-Dayel F, Uddin S, Al-Kuraya K. Fatty acid synthase inhibition suppresses p-AKT and induces apoptosis in colorectal carcinoma. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
- Hussain A, Ahmed M, Al-Jomah N, Khan A, Ahmed S, Sultana M, Manogaran P, Abubaker J, Platanius L, Al-Kuraya K. Curcumin requires

- constitutive activation of NF κ B and functional Bax to induce apoptosis in Burkitt's lymphoma cell lines. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
- Khan S, Hussain A, Ahmed M, Plataniias L, Uddin S, Al-Kuraya K. Apigenin down-regulates constitutive activation of AKT and induces apoptosis in primary effusion lymphoma cells. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
 - Ahmed M, Hussain A, Bavi P, Ibrahim M, El-Sayed R, Munkarah A, Uddin S, Al-Kuraya K. Apoptosis induced by aspirin via inhibition of AKT activity and downregulation of cyclooxygenase 2 expression. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
 - Ahmed M, Hussain A, Bavi P, Ibrahim M, El-Sayed R, Munkarah A, Uddin S, Al-Kuraya K. Proteasome inhibitor Bortezomib (Velcade[®]) induces apoptosis via degradation of SKP2 in ovarian cancer. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
 - Al-Kuraya K. Proteasome pathway is an attractive target for colorectal cancer therapy. BIT's Annual World Cancer Congress 2008, June 12-17, 2008, Everbright Convention & Exhibition Center, Shanghai, China.
 - Siraj AK, Al-Rasheed M, Ahmed M, Ibrahim M, Al-Nuaim A, Al-Dayel F, Bavi P, Hussain A, Uddin S, Al-Kuraya K. Fatty acid synthase is a potential target for a subset of papillary thyroid cancers. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
 - Siraj AK, Al-Rasheed M, Ibrahim M, Al-Dayel F, Uddin S, Al-Kuraya K. RAD52 polymorphisms contribute to the development of papillary thyroid cancer susceptibility in Middle Eastern population. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
 - Abubaker J, Bavi P, Al-Harbi S, Ibrahim M, Al-Hagawi W, Al-Sanea N, Abduljabbar A, Ashari L, Alhomoud S, Al-Dayel F, Uddin S, Al-Kuraya K. PI3K/AKT and MAPK pathways cross talk and their possible role in CRC tumorigenesis of Middle Eastern population. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
 - Al-Kuraya K, Uddin S, Bavi P, Al-Dayel F, Al-Sanea N. Leptin Receptor Expression in Middle Eastern Colorectal Cancer and Its Potential Clinical Implication. AACR Targeting the PI3-Kinase Pathway in Cancer, November 11-14, 2008, Massachusetts, USA.
 - Al-Kuraya K, Uddin S, Maqbool A, Hussain AR, Al-Dayel F, Al-Sanea N. Genetic Look at Middle Eastern Colorectal Cancer. 8th International Conference of Anticancer Research, October 17-22, 2008, Kos, Greece.
 - Abubaker J, Jehan Z, Bavi P, Sultana M, Ibrahim M, Al-Nuaim A, Ahmed M, Amin T, Al-Fehaily M, Al-Sanea O, Al-Dayel F, Uddin S, Al-Kuraya K. Clinicopathological analysis of papillary thyroid cancer with PIK3CA alterations in Middle Eastern population. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
 - Uddin S, Hussain A, Ahmed M, Khan A, Bavi P, Al-Kuraya K. Proteasome inhibitor MG-132 induces p27Kip1 expression through SKP2 degradation in diffuse large B cell lymphoma. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
 - Uddin S, Ahmed M, Bavi P, Al-Sanea N, Abduljabbar A, Ashari L, Alhomoud S, Al-Dayel F, Hussain A, Al-Kuraya K. Bortezomib (Velcade) induces p27kip1 associated cell cycle arrest and apoptosis through down-regulation of SKP2 ubiquitin ligase pathway in colorectal carcinoma.

- AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
- Bavi P, Ahmed M, Devarajan S, Moorji A, Atizado V, Balde V, Abduljabbar A, Alhomoud S, Ashari L, Alsanea N, Uddin S, Al-Kuraya K. Leptin-R is an independent prognostic marker in colorectal carcinoma. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
 - Bavi P, Siraj AK, Al-Rasheed M, Devarajan S, Atizado V, Ahmed M, Amin T, AlNuaim A, Uddin S, Al-Kuraya K. Leptin and Leptin-R expression in papillary thyroid carcinoma. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
 - Bavi P, Devarajan S, Atizado V, Balde V, Siddiqui S, Moorji A, Al-Dossary H, Ezzat A, Al-Dayel F, Uddin S, Al-Kuraya K. Reduced or absent cyclin dependant kinase (CAK) expression is an independent prognostic marker for poor outcome in diffuse large B cell lymphoma. AACR Annual Meeting 2008, April 12-16, 2008, San Diego Convention Center, San Diego, California, USA.
 - Al-Kuraya K. Fatty Acid Synthase is a potential therapeutic target in Microsatellite-instable colorectal cancers. *Advances in Cancer Research: From the Laboratory to the Clinic*, March 16-19, 2008, King Hussein Bin Talal Convention Center, Dead Sea, Jordan.
 - Al-Kuraya K. Ubiquitin-ligase SKP2 pathway is an attractive target for colorectal cancer therapy. 1st International Conference on Drug Design & Discovery, 3-6 February 2008, Dubai, UAE.

THE STEM CELL
THERAPY PROGRAM

The Stem Cell Therapy Program

Stem Cell Therapy Program (SCTP) at the Research Centre focuses on researching the cellular and molecular mechanisms of stem cells and stem cell applications in the treatment of a number of chronic diseases including cardiovascular diseases, neuro-degenerative diseases & spinal cord injuries, liver diseases, kidney diseases, diabetes, autoimmune diseases, and cancer. SCTP runs quality research laboratories equipped with the latest technologies and powered with a team of scientists and technicians towards achieving excellence in the field of stem cell research in Saudi Arabia, the Middle-East and worldwide.

Director:

Chaker N. Adra, PhD

Administrative Support Staff:

Madeline Fiji S. Ranera

Mary Jane S. Anonuevo

LIST OF SIGNIFICANT ACHIEVEMENTS

- Established an independent unit to study stem cell biology in collaboration with The Transplantation Center at Harvard Medical School.
- Successfully recruited a world wide expert in Transplantation and Stem Cell Therapy, Dr. 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, who was employed in our Program as Adjunct Principal Scientist and now became the Vice President of Medical Affairs, and Dean of the Faculty of Medicine at the American University in Beirut Medical Center (AUBMC).
- Signed two (2) Memoranda of Understanding with two prestigious institutions:
 - ∞ Harvard Medical School (USA), 19th of January 2008.
 - ∞ INSERM and University Hospital Center (France), 4th of November 2007.

-
- Four (4) Patent Applications;
 - ∞ “Methods and Compositions for Cell-Cycle Regulation”- A0852.70001US2, App Patent No. - 11/77938, Published 26 June 2008, USA
 - ∞ “Granulocyte Subtype-Selective Receptors and Ion Channels and Uses Thereoff” - A0852.70000US1, App Patent No. - 10/591628, Published: 07-Aug-2008, USA
 - ∞ “HTM4UsedforCell-CycleRegulation Through its Interaction with KAP” – A0852.70001CN00, App Patent No.- 200680008602.5. Published: 12 Mar-2008, China
 - ∞ “HTM4 Used for Cell-Cycle Regulation Through its Interaction with KAP” – A0852.70001EP00, European Patent Covention, App Patent No.- 0671885204. Published: 16 Jan-2008
 - Launched the first clinical trial entitled: Stem Cell Therapy in Patients with Severe Peripheral Arterial Disease of the Lower Limps.
 - 2 Symposiums & Workshops Organized;
 - ∞ Basic Proteomics Course & Mass Spectrometry Workshop, 25-27 Oct. 2008 Basic Stem Cell Course, 27-30 Dec. 2008
 - Supported young Saudi Arabian researchers in pursuing training/higher education and postdoctoral fellowships at respected international institutes;
 - ∞ 2 Post Doctoral Harvard Fellow at Harvard Medical School
 - ∞ 1 Post Doctoral Fellow at the University of South Paris
 - ∞ 3 PhD Scholarship at Imperial College London, United Kingdom
 - ∞ 1 Post Doctoral Fellow at the University of Portsmouth, United Kingdom
 - ∞ 1 Post Doctoral Fellow at the Toronto Institute, Canada
 - ∞ 1 MSc in Stem Cell Technology at the University of Nottingham
 - ∞ 5 Students being interviewed and competing for PhD program at Imperial College, London
 - Established scientific collaborations with multiple institutions both national and international with combined scientific and experimental efforts towards achieving the goal of excellence in stem cell research in the Middle East area and worldwide;
 - ∞ Massachusetts General Hospital
 - ∞ Brigham and Women’s Hospital
 - ∞ Children’s Hospital Boston
 - ∞ Harvard Medical School
 - ∞ Harvard University
 - ∞ Karolinska, Sweden
 - ∞ Dubai Harvard Foundation for Medical Research
 - ∞ Imperial College, United Kingdom
 - ∞ Department of Pathology and Laboratory Medicine
 - ∞ Department of Urology
 - ∞ Department of Medicine
 - ∞ Renal Transplant Program
 - ∞ Cord Blood Bank, Department of Pathology and Laboratory Medicine
 - ∞ Department of Neurosciences
 - ∞ Prince Salman Centre for Disability Research
 - ∞ King Saud University
 - ∞ Prince Fahad bin Salman Charity Association for Renal Failure Patients Care
 - The Stem Cell Therapy Program runs quality research laboratories equipped with the latest technology and powered with a team of scientists and technicians towards achieving excellence in the field of stem cell research in Saudi Arabia, Middle-East and worldwide;
 - ∞ FACSArray Bioanalyzer
 - ∞ FACSAria Cell Sorting Unit
 - ∞ Pathway 855 Bioimager-Automated Cell Imaging Assay System
 - ∞ MALDI-TOF MS (Matrix Assisted Laser Desorption Time of Flight Mass Spectrometry)
 - ∞ Synapt High Definition Tissue Imaging Mass Spectrometry
 - ∞ JANUS Automated Robotic Mass Prep Station
 - ∞ Proteome Works Spot cuter

- ∞ Typhoon Trio Variable Mode Fluorescent Scanner
- ∞ Cell Separator Fully Automated System (SEPAXNET)
- Twenty three (23) Stem Cell Therapy Program (Approved) Research Projects. Two (2) Projects was recently approved for KACST funding;
 - ∞ Identification and Therapeutic Targeting of ABCB5+ Tumor Stem Cells (RAC #2080 023)
 - ∞ Stem Cells Interactions with the Inflammatory Environment in Multiple Sclerosis and other Neurodegenerative Diseases of the Central Nervous System (RAC # 2070 018)

RESEARCH ACTIVITIES

Project Title: Development of Autologous Stem Cell Therapy for Patients With Severe Peripheral Arterial Disease of the Lower Limbs-A Phase II Non-Randomized Study, RAC # 2081 021.

Principal Investigator: Dr. Chaker Adra

Co-Principal Investigators: Dr. Nahar Al-Anezi and Dr. Hind Al-Humaidan

Co-Investigators: Dr. Saleh Al-Othman, Dr. Ayodele Alaiya, Dr. Fouad Hassan Al-Dayel, Dr. Tauqir Ahmed Rana, Dr. Morad Al-Kaff, Dr. Tarek Al-Owaidah
Dr. Bassel Safi,

Advisors: Dr. Mohamed H. Sayegh and Dr. Michael S. Conte

PROJECT DESCRIPTION

The primary aim of this study is to use autologous transplantation of mononuclear stem cells (MNCs) derived from either bone marrow (BM) or peripheral blood from patients with severe Critical Limb Ischemia (CLI) and to assess the efficacy, safety and feasibility of treatment protocol. The study in addition; aims to identify Peripheral Arterial Disease (PAD)-associated biomarkers using global protein expression analysis.

METHODS

Twenty patients diagnosed with CLI; that are not amenable to any intervention or bypass-able patients with high risk for surgery will be recruited for the study.

MNCs will be sorted in the lab either from harvested iliac crest BM or from peripheral blood. MNCs will then be injected either intramuscular alone in the calf of the ischemic leg or in combination with intra-arterial injection via the femoral artery of the ischemic leg. Patients will be assessed for 3 to 12 months post transplantation to the outcome of the treatment.

We will also use proteomics approaches to identify potential biomarkers from tissue biopsies and blood samples that could be useful in the development of Stem Cells for therapeutic strategies in regenerative disorders and arterial occlusive diseases.

SIGNIFICANCE

The outcome of this clinical trial will improve our understanding of the potential use of Stem Cell therapy as an alternative intervention for patients with severe PAD. In addition, association between results from benchwork with results obtained in the clinical trial will further assist the identification of cellular and molecular PAD-associated biomarkers, towards improving diagnosis of PAD and developing better treatment strategies.

PROGRESS/ MAJOR FINDINGS

The project was recently approved and patient recruitment have commenced. To enhance adequate number of patient accrual, we are contacting peripheral Saudi Arabia hospitals to refer patients who meet the study inclusion criteria. It is anticipated that we will administer stem cell injections to the first one or two patients before summer of 2009.

Project Title: Expansion and Differentiation of Human Embryonic and Hematopoietic Stem Cells Using Proteomics: The Therapeutic Use of Stem Cells in Disability Research, RAC #2080 050.

Principal Investigator: Dr. Chaker Adra

Co-Investigators: Dr. Judith Nagy, Dr. Hind Al-Humaidan, Dr. Ayodele Alaiya, Dr. Andrew Wetzig, Dr. Maha Al-Mozaini, Dr. Saleh Al-Othman, Mr. Pulicat S. Manogaran, Dr. Hazem Ghebeh

PROJECT DESCRIPTION

A primary goal of this work is to find new ways to identify stem cells and discover what sort of media they need for growth *in vitro* and how to differentiate them reproducibly into variable specific cell lineages. We will look at how different molecules changes using high-throughput proteomics to map the cellular protein profile and the secreted proteins in the culture media to develop standardized protocols for reproducible tissue engineering. We are also going to label these proteins with fluorescent dyes and compare the protein profile of the starting material with the cultured cells (this is called differential two dimensional gel electrophoresis, DIGE) and use this to follow changes in stem cells as they grow and differentiate and give an intelligent feed-back system of how protein regulation is changing as the culturing conditions are varied.

This is a collaborative research project between the Proteomics Facility of the Stem Cell Therapy Program at KFSH&RC, Riyadh, Saudi Arabia and the Proteomics Facility at Imperial College, London with a major aim to help the growing number of individuals suffering from disability in Saudi Arabia. Integration of proteomic studies carried out at the two complementary proteomics centers will serve the purpose of stem cell characterization for clinical applications.

PROGRESS

This is a recently approved project and the hESC will be obtained from the UK Stem Cell Bank following the approval of the UK Stem Cell Steering Committee.

Project Title: Investigating the Immunogenicity of Breast Cancer Stem Cells, RAC # 2080 045.

Principal Investigator: Dr. Chaker Adra

Co-Investigators: Dr. Hazem Ghebeh, Dr. Monther Al-Alwan, Dr. Taher Al-Tweigeri, Dr. Khalid Al-Faqeeh, Cynthia Lehe and Ghida Sleiman

PROJECT DESCRIPTION

In this proposal, we will study how cancer stem cells effect antigen presentation and immune response generation. We will also investigate the role of CSC in the creation of

immune suppressive microenvironment which finally leads to tumor escape from the immune system surveillance.

The outcome of this study should provide an attractive approach to treat cancer by targeting the cancer stem cells using vaccines against their antigens or chemotherapy that is able to clear this population and/or alter their immunogenicity.

PROGRESS

This project has just been approved. Currently we are collecting samples from normal breast tissues and tumor tissues from breast cancer patients.

Project Title: Genetic Basis of Kidney Disease in the Kingdom of Saudi Arabia, RAC # 2080 042.

Principal Investigator: Dr. Chaker Adra

Co-Principal Investigator: Dr. Martin Pollak

Co-Investigators: Dr. Khaldoun Al-Romaih, Dr. Saleh Al-Othman, Dr. Hamad Al-Mojalli, Dr. Hadeel Al-Manea, Dr. Mai Al-Mohanna, Noura Atallah, Alia Iqniebi

PROJECT DESCRIPTION

The focus of this collaborative research is on kidney nephropathies, with a particular interest in the study of the genetics, and epigenetics of renal diseases and the potential application of stem cells for novel therapies. In the first project in this collaborative effort we are recruiting families with kidney disease to determine if defects in known genes can account for the disease by analysis of DNA sequence and to explore the possibility of identifying novel disease causing mutations/genes. In families in which multiple members share the same kidney disease, we are using genetic linkage analysis to identify chromosomal regions that are associated with the disease inheritance. We will then identify the specific DNA change within these regions.

PROGRESS

In collaboration with consultants from the Pediatrics and Pathology departments at the KFSH&RC and scientists from Harvard, Boston, the project was launched on January 2009 and 20 families were enlisted. 28 individuals from 8 families were already recruited and DNA, RNA and serum

was extracted from the blood samples of these individuals. The team continues to ascertain families with kidney disease and, more importantly, to extend the number of participants from the families already enlisted in order to increase the power of genotyping/linkage analysis that we intend to perform. Primers for a number of genes that are known to cause kidney nephropathies have been designed (including primers for ACTN4, NPHS1, NPHS2, and TRPC6) and DNA amplification followed by sequencing is ongoing. The project was also the basis on which collaboration was initiated between Dr. Chaker Adra (Director, SCTP-RC) and Dr. Martin Pollak at the Renal Divisions of the Brigham and Women's Hospital BWH- Harvard Institutes of Medicine in Boston, USA. In addition Dr. Adra supported a Scholar Researcher –Fellowship position at BWH-Harvard for a Saudi Arabian postdoctoral fellow from the SCTP in the aim of conducting some of the work described in the project in one of the leading labs in Kidney Failure diseases in the world (Dr. Pollak's lab, BWH-Harvard).

Project Title: Investigating the Role of Cellular Inhibitory Proteins in Eosinophils Apoptosis: Implication in Asthma/Atopy, RAC #2080 026.

Principal Investigators: Dr. Bandar Al-Saud and Dr. Chaker Adra
Co-Investigators: Dr. Ayodele Alaiya, Dr. Monther Al-Alwan, Dr. Hind Al-Humaidan and Eman Barhoush

PROJECT DESCRIPTION

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

PROGRESS/MAJOR FINDINGS

1. This proposal is only recently approved and the required reagents and antibodies have been ordered

2. The optimal PCR conditions have been optimized on the Jurkat cell line, which are positive for c-FLIP
3. Recruitment of asthmatic patients is ongoing

Project Title: Identification and Therapeutic Targeting of ABCB5+ Tumor Stem Cells, RAC #2080 023.

Principal Investigator: Dr. Chaker Adra

Co-Investigators: Dr. Dahish Ajarim, Dr. Fouad Hassan Al-Dayel, Dr. Ayodele Alaiya, Dr. Asma Tulba, Dr. Tarek Amin, Dr. Imaduddin Kanaan and Dr. Hazem Ghebeh

PROJECT DESCRIPTION

Cancer stem cells capable of self-renewal and differentiation, which are involved in tumor growth and progression, have been identified in human hematological malignancies and several solid cancers. We hereby propose to explore the clinical relevance of ABCB5 as a biomarker of tumor stem cells and of cancer progression, prognosis, and outcome in diverse human malignancies demonstrated to express ABCB5. In addition, we propose to explore the therapeutic efficacy of ABCB5 targeting strategies in relevant animal models of such cancers. This approach will determine the clinical relevance and therapeutic importance of this novel biomarker, and should pave the road to eventual clinical therapeutic trials focused on targeting of ABCB5-positive tumor stem cells.

PROGRESS

This project has just been approved. Currently we are collecting samples from normal breast tissues and tumor tissues from breast cancer patients.

Project Title: Proteomic Analysis of Human Breast Cancer Stem/Progenitor Cells, RAC # 2080 021, (Proteomics).

Principal Investigator: Dr. Ayodele Alaiya

Co-Principal Investigator: Dr. Chaker Adra

Co-Investigators: Dr. Fouad Al-Dayel, Dr. Hind Al-Humaidan, Dr. Dilek Colak, Dr. Ghebeh Hazem, Dr. Asma Tulba, Dr. Taher Al-Tweigeri, Prof. Godovac-Zimmermann J. and Layla Al-Mansouri

PROJECT DESCRIPTION

The goal of this study is to investigate the critical molecular alterations affecting breast cancer stem cells, and how they interact with their microenvironment. The phenotypic characteristics of mammary stem cells will be defined at the protein level using a proteomics approach. This will provide information which could be used to improve both the diagnosis of breast cancers and the ability to predict clinical outcomes and response to the current treatment modalities. Furthermore, new selective therapeutic strategies could be developed targeting breast cancer stem cells while sparing normal stem cells.

This is a PhD student's project in collaboration with University College London.

PROGRESS/MAJOR FINDINGS

1. Breast cancer tissue samples have been obtained from 6 patients
2. All collected samples, so far, have been processed for isolation of epithelial cells
3. Dissociated cell culture was attempted on one sample and protocol optimization is ongoing.
4. Sorting of the tissue mammary epithelial cells is being optimized.
5. The cell extraction method for the isolation of stem cells is currently being optimized.
6. The cell extraction method and optimization for proteomics analysis is ongoing.

Project Title: The Propagation of Mesenchymal and Neural Stem Cells from Adult Olfactory Mucosa, RAC # 2080 007.

Principal Investigator: Dr. Chaker Adra

Co-Investigators: Dr. Ayodele Alaiya, Dr. Andrew Wetzig, Dr. Hind Al-Humaidan and Dr. Imaduddin Kanaan

PROJECT DESCRIPTION

The overall aim of this project is to develop a therapeutic adult stem cell treatment for spinal cord injuries. Both mesenchymal and neural stem cells could be harvested from the patient's olfactory mucosa and used together to treat the injured spine. In this way the

immunosuppressive and neurotrophic properties of mesenchymal stem cells (MSCs) would be combined with the ability of neural stem cells to differentiate into replacement neurons. The aims of this project are to 1) determine the presence of MSCs in the olfactory mucosa, 2) compare olfactory MSCs with MSCs derived from the bone marrow and umbilical cord, known sources of MSCs.

PROGRESS

1. 51 Olfactory biopsies have been processed - 17 patients x 3 biopsies per patient
2. 49 umbilical cords and 3 bone marrow samples processed
3. Dissociated cell cultures have been established from all three tissue samples. However, optimization of the cell extraction methods for olfactory biopsies and umbilical cords is ongoing.
4. Cultured olfactory cells express MSC markers and demonstrate a phenotype similar to bone marrow and umbilical cord cultures.
5. Olfactory cells failed to differentiate into chondrocytes, adipocytes and osteocytes, a defining feature of MSCs - Olfactory cells demonstrate the phenotype but not the function of MSCs
6. Human olfactory tissue sections are positive for MSC markers and demonstrate variable expression patterns.

Project Title: Neurosteroids and Alzheimer's Disease: Protection against Beta-Amyloid Peptide-Induced Toxicity in Neuronal Cells, RAC # 2080 005.

Principal Investigator: Dr. Fadia El-Bitar

Co-Investigators: Dr. Chaker Adra and Dr. Yvette Akwa

PROJECT DESCRIPTION

The pathophysiology of Alzheimer's disease is thought to be attributable to the effects of β -amyloid ($A\beta$) peptides that accumulate in the brain causing neurotoxicity and neurodegeneration. Our work is based on the use of natural pregnenolone sulfate

(PREGS) that has previously been shown to enhance memory performance in rodents (Akwa et al. 2001). Our objective is to investigate *in vitro* if PREGS has neuroprotective activity against A β peptide-induced neurotoxicity, using rat neuroblastoma B104 as cell culture model.

PROGRESS/ FINDINGS

1. A dose–response study for PREGS in cultured B104 cells showed that PREGS is not neurotoxic per se.
2. PREGS showed a striking neurotrophic activity in cells cultured at low density.
3. We showed the neurotoxicity of the fibrillary form of human A β 1-42 peptide (fA β 1-42), i.e. 10 μ M of fA β 1-42 was able to induce a significant necrotic effect on B104 cells after 6h treatment, compared to control cells.
4. Most importantly, we demonstrated the capacity of PREGS to correct fA β 1-42 neurotoxicity, thus revealing neuroprotective properties of PREGS against the A β peptide.

Overall, treatment with a specific neuroactive steroid such as PREGS that counteracts the neurotoxic effects of A β peptide may be promising against neurodegeneration in Alzheimer's disease.

Project Title: Stem Cells Interactions With the Inflammatory Environment in Multiple Sclerosis and other Neurodegenerative Diseases of the Central Nervous System, RAC # 2070 018.

Principal Investigator: Dr. Chaker Adra

Co-Investigators: Dr. Ayodele Alaiya, Dr. Imaduddin Kanaan, Dr. Mai Al-Mohanna, Dr. Samia Khoury, Dr. Tarek Amin and Kholoud Al-Saud

PROJECT DESCRIPTION

Aims of the study

- To examine the effect of Interferon (IFN)-gamma and the transcription factor STAT1 on the self-

renewal program of Neural Stem Cells (NSCs) *in vivo* and on their molecular program *in vitro*.

- To examine the effect of IFN-gamma on the migration of NSCs *in vivo* and on their molecular program *in vitro*.
- To examine the effect of STAT1 on the differentiation of NSCs *in vivo* and on their molecular program *in vitro*.

Methods

Several animal models will be used to determine the effect of STAT1 deficiency in NSCs in an inflammatory environment. This includes the use of STAT1 knockout mice and adaptive transfer of GFP-labeled STAT1-KO NSCs into wild type mice with Experimental Autoimmune Encephalomyelitis. To determine the effect of Interferon-gamma on NSCs migration *in vivo* in an inflammatory environment, IFN-gamma-KO GFP-labeled NSC will be adaptively transferred to wild type mice. Samples will also be subjected to proteome analysis using 2-DE, protein chips and mass spectrometry. Using these methods, the effect of STAT-1 and IFN-gamma genes on NSCs self-renewal capacity and migration will be assessed.

Significance

Human embryonic stem cells represent great hope for successful treatment of diseases in the future including; Multiple Sclerosis, Alzheimer's Disease, Parkinson's Disease, Spinal Cord Injuries, Diabetes and Cardiovascular Disease. There is particular interest in using stem cells in the treatment of neurological disorders, because these injuries are permanent due to the irreversibility of neuronal damage. In light of the lack of treatment for Multiple Sclerosis, the promise of stem cell therapy offers great hope in tissue repair, replacement and regeneration that will lead to new clinical innovations and revolutionize Personalized Medicare.

PROGRESS/MAJOR FINDINGS

The project was recently approved and animal experiments have been commenced.

Project Title: Proteomics Approach to Biomarker Discovery in Aplastic Anemia, RAC #2060 021.

Principal Investigators: Dr. Ayodele Abdulkareem Alaiya and Dr. Mahmoud Al-Jurf

Co-Principal Investigators: Dr. Naeem Chaudhri and Dr. Hazzaa Al Zahrani

Co-Investigators: Dr. Mai Al-Mohanna, Dr. Entezam Sahovic, Dr. Fahad Al Mohareb, Dr. Fahad AL Sharif, Dr. Hamad Al Omar and Dr. Ali Al Shanqeeti

PROJECT DESCRIPTION

We will analyze global protein expression profiles in patients with aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH) and hypoplastic myelodysplastic syndrome (MDS). The goal is to identify novel protein biomarkers that can differentially diagnose various bone marrow failure syndromes and provide accurate patient stratification for treatment.

PROGRESS

1. 16 samples collected (AA=8, MDS=3, PNH=1, NBM=1, 3 =pending pathology report. Sample processing/ optimization have been completed.
2. Comprehensive data analysis has commenced.
3. 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, South Korea Oct.2007.
4. Protein identification work by MALDI-TOF-MS has commenced.

Project Title: Investigating the Role of the Actin Bundling Protein (fascin) in Regulating Dendritic Cell Migration and Breast Cancer Metastasis in Saudi Population, RAC # 2060 016.

Principal Investigator: Dr. Monther Al-Alwan

Co-Investigators: Dr. Hazem Ghebeh, Dr. Asma Tulbah, Dr. Taher Tweigeri, Dr. Dahish Ajarim and Dr. Mahmoud Al Jurf

PROJECT DESCRIPTION

The cytoskeleton has been reported to regulate cell's morphology and motility. The actin-bundling protein,

fascin, is a member of the cytoskeletal protein family. While it has restricted expression in specialized normal cells, many studies have reported fascin expression in various transformed cells including breast cancer. The exact role of fascin in breast cancer cells has not been fully understood. The main aim of this proposal is to examine whether fascin induction in breast cancer facilitates metastasis and delineates the underlying mechanism.

PROGRESS/MAJOR FINDINGS

1. An abstract was published at the Advance in Cancer Research: From Laboratory to the Clinic, Dead Sea, Jordan (March 2008) Direct correlation between fascin expression and breast cancer metastasis Monther Al-Alwan¹, Hazem Ghebeh, Eman Barhoush, Asma Tulbah, Taher Tweigeri, Dahish Ajarim, Ayodele Alaiya, Mahmoud Aljurf, Said Dermime. Stem Cell Therapy Program, Departments of Pathology, Oncology, Adult Hematology/Oncology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
2. A poster was presented during the above mentioned meeting Fascin regulate breast cancer metastasis via up-regulated secretion of Matrix Metalloprotease and suppression of Breast Cancer Metastasis Suppressor 1 Monther Al-Alwan, Safiah Olabi, Hazem Ghebeh, Eman Barhoush, Asma Tulbah, Taher Tweigeri, Dahish Ajarim, Ayodele Alaiya, Chaker Adra. Stem Cell Therapy Program, Departments of Pathology, Oncology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
3. Fascin regulation of breast cancer cell morphology, migration and invasion has been established
4. Inhibition of fascin in breast cancer cells by chemotherapy, leading to reduction in migration and invasion was observed.
5. Identifying the molecular mechanism of fascin regulation of breast cancer migration and invasion is ongoing.
6. A manuscript is in preparation.

Project Title: Clinical Proteomics: Development of Novel Biomarkers for Diagnosis of Ovarian Cancer, RAC # 2050 043, Funded By KACST.

Principal Investigator: Dr. Ayodele Abdulkareem Alaiya

Co-Principal Investigator: Dr. Mai Al-Mohanna

Co-Investigators: Dr. Hany Al-Salem, Dr. Ismail Al- Badawi, Dr. Jamal Al-Subhi, Dr. Nada Al- Sahan, Dr. Asma Tulba MD and Dr. Osama Al-Omar

PROJECT DESCRIPTION

The goal of this work is to develop tools for the accurate classification of borderline tumors and differential diagnosis of pelvic tumor of unknown primary origin. We are using mini-2-DE gels technology which are rapid, simple and sensitive, thus making it especially applicable for routine tumor diagnosis.

Protein spots that differ significantly in their expression between benign and malignant tumors will be identified and used for objective and accurate molecular classification of borderline ovarian tumors and in particular in the differential diagnosis of borderline tumors and carcinomas.

PROGRESS

1. Preliminary analysis of samples is ongoing.
2. A database of different types of pelvic mass is being generated through computer assisted image analysis.
3. Preliminary data showed that tumors of different malignant grades can be discriminated based on their protein expression patterns.

Project Title: Chronic Myeloid Leukemia: Development and Validation of Therapeutic Hematoproteomic Biomakers, RAC #2050 040, (Proteomics).

Principal Investigator: Dr. Ayodele Abdulkareem Alaiya

Co-Principal Investigators: Dr. Mahmoud Al-Jurf and Dr. Naeem Chaudhri

Co-Investigators: Dr. Mai Al-Mohanna, Dr. Entezam Sahovic, Dr. Fahad Al Mohareb, Dr. Fahad Al Sharif, Dr. Hamad Al Omar, Dr. Hazzaa Al Zahrani and Dr. Ali Al Shanqeeti

PROJECT DESCRIPTION

This project focuses on the analysis of global protein expression profiles in patients with Chronic Myeloid Leukemia in the chronic phase (CP CML). Peripheral blood (plasma/serum) and bone marrow samples from the same patients will be analyzed using 2-D gel electrophoresis and computer-assisted image analysis. Proteins of interest will be identified by peptide mass fingerprinting and sequencing. The goal is to identify novel protein biomarkers that will predict therapy response or disease resistance. This information will assist clinicians to develop customized treatment plans for patients individually.

PROGRESS/FINDINGS

1. Sample processing/ optimization has been completed.
2. Preliminary analysis has commenced.
3. An abstract was published during 6th HUPO Annual World Congress held in Seoul, South Korea Oct.2007.
4. Sample collection is on going (Thirty six samples have been collected so far). Chart review for extraction of clinico-pathological data for correlation of clinical features with protein expression patterns is on going.
5. Poster was presented during the above named congress.
6. Bone marrow plasma proteome is more enriched than BM serum

Project Title: Study of the Association between HLA-DRB1 Alleles and Vogt-koyanagi-Harada's Disease in Saudi Patients, RAC # 2050 034.

Investigators: Khaled Al-Hussein and Khaled Tabara

PROJECT DESCRIPTION

Vogt-Koyanagi-Harada (VKH) disease is a potentially blinding disorder that afflicts the uvea in the eye leading to chronic inflammation. Associations with other auto-immune disorders have been reported. In Saudi Arabia, VKH has been found to be a common cause of uveitis as previously reported by Islam and Tabbara. Previous reports indicate certain HLA genotypes show strong association with DRB1 *0405 and DRB1 *0410 and confer increased

risk of VKH disease. It has been suggested that the HLA DRB1 gene is one of the candidate genes of VKH.

PROGRESS/MAJOR FINDINGS

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. In conclusion, 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.

PROJECT DESCRIPTION

The gene expression of prostate tumors at the protein level will be studied by means of 2-D gel electrophoresis and computerized image analysis. The focus of this project is on the complex protein expression pattern of human prostate tumors, of varying malignancy potential, to identify proteins related to tumorigenesis, grade of

aggressiveness, metastatic potential and treatment sensitivity. The aim is to find a correlation between altered tissue morphology and polypeptide expression. Ultimately this would complement the diagnostic markers already in the use, and commence a wider scan of the prostate proteome for carcinoma specific markers. Novel proteins will

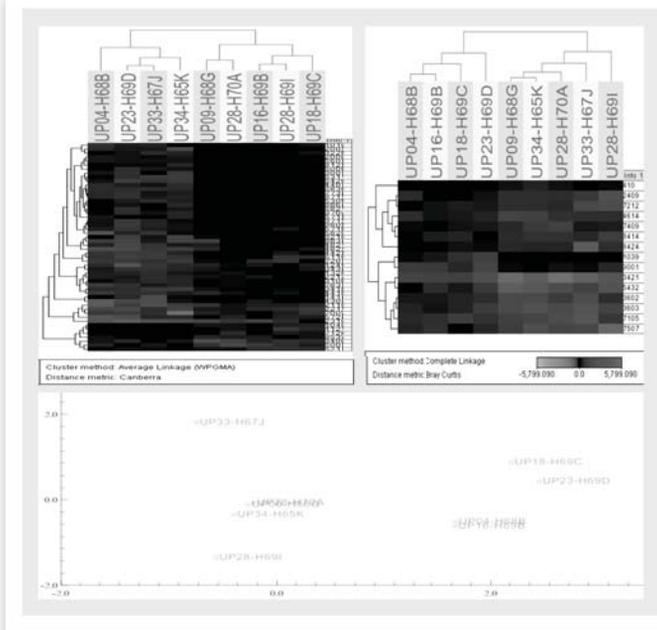


Figure 1: Hierarchical cluster analysis of sets of proteins that are statistically differentially expressed between Gleason 6 vs. Gleason 7 tumors (A) and between T2 vs. T3 prostate carcinomas (B). Corresponding analysis of the Gleason score data set is shown in (C).

be characterized by highly sensitive mass spectrometry and if necessary sequence analysis.

Project Title: Clinical Cancer Proteomic: Understanding the Cellular and Molecular Biology of Prostate Tumors, RAC # 2050 026.

Principal Investigator: Dr. Ayodele Abdulkareem Alaiya
Co-Principal Investigator: Dr. Ali Bin Mahfooz
Co-Investigators: Dr. Mai Al-Mohanna, Dr. Mohammad Aslam, Dr. Irfan Ahmed and Dr. Kamal Hanash

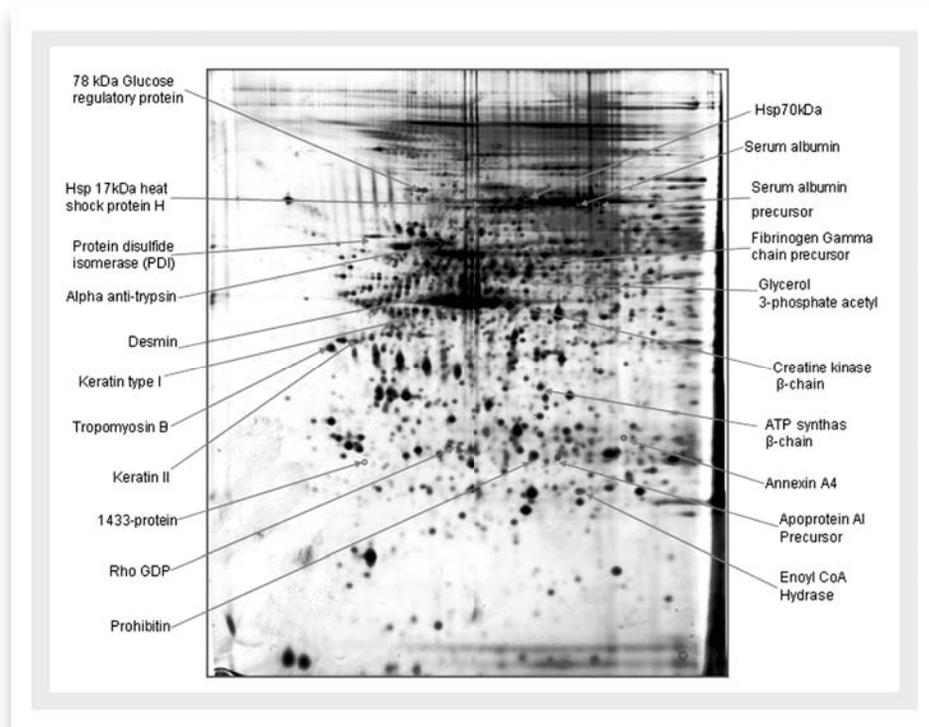
PROGRESS

1. Our data showed that we can discriminate benign from malignant prostate tumors as well as tumors of low and high malignancy grades based on their protein expression patterns (Figure 3).
2. We have identified (by MALDI TOF-MS) more than 20 proteins with significant differentially expression patterns between malignant tumors of

different histological grade and stage. Some of the identified proteins are marked in the figure 4.

3. Abstract/poster accepted for presentation during 1st International Biotechnology Conference Feb 16-18, Riyadh, KSA.
4. A Manuscript is in preparation.

tumor model. The 4T1 mammary carcinoma cell line is transplantable and tumors grow both in nude and BALB/c mice and in tissue culture. In addition the cells give rise to tumors that are invasive and that easily metastasize to distant sites, thus mimicking human mammary cancer. Complex protein mixtures from



Project Title: Protein Profiling: Understanding the Mechanisms of Tumor Responses to Therapy in a Mouse Model, RAC # 2050 014.

Principal Investigator: Dr. Ayodele Abdulkareem Alaiya

Co-Investigators: Dr. Mai Al-Mohanna, Dr. Raafat El-Sayed, Dr. Falah Al-Mohanna

PROJECT DESCRIPTION

This pilot study is based on a mouse 4T1 breast

Figure 2: A representative 2-DE map derived from a prostate cancer sample. Marked are some of the identified proteins that differ between sample sub types. The proteins were identified by MALDI-TOF Mx Micro (Waters®, UK).

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. An abstract was published during 5th HUP0 world

congress at Long Beach California, 28th Oct -1st Nov 2006.

2. A poster was presented during the above mentioned meeting.
3. Protein identification by MALDI-TOF MS has commenced and more than 10 proteins have been identified from tissue samples. Comparison of identified proteins from tissue and serum samples is ongoing.
4. Abstract/poster accepted for presentation during 1st International Biotechnology Conference Feb 16-18, Riyadh, KSA.
5. A manuscript is in preparation

Project Title: Clinical Proteomics: Development of Novel Biomarkers for Translational Ovarian Cancer Research, RAC # 2050 011.

Principal Investigator:

Dr. Ayodele Abdulkareem Alaiya

Co-Principal Investigator:

Dr. Mai Al-Mohanna

Co-Investigators:

Dr. Ismail Al-Badawi, Dr. Hany Al-Salem, Dr. Jamal Al-Subhi, Dr. Nada Al-Sahan, Dr. Asma Tulba and Dr. Osama Omar

PROJECT DESCRIPTION

This project focuses on the analysis of global protein expression profiles in patients diagnosed with sporadic common epithelial ovarian tumor that are treated with conventional surgical and adjuvant therapy and/or cytoreductive and radiation therapy. The goal is to identify novel protein biomarkers capable of predicting patient's response to therapy and clinical outcome.

PROGRESS

1. Over 60 samples have been collected and about 1/3 of the cases
2. Incomplete data on clinical reports has delayed selection of interesting protein spots for identification

by mass spectrometry
3. Protein identification by MALDI-TOF MS (>60 proteins identified).

4. Preliminary data showed that tumors of different malignant grades can be discriminated based on their protein expression patterns.

5. Significant progress towards development of a data base for

artificial disease classification based on differentially expressed proteins and efficient data mining has been made (Figures 3 & 4).

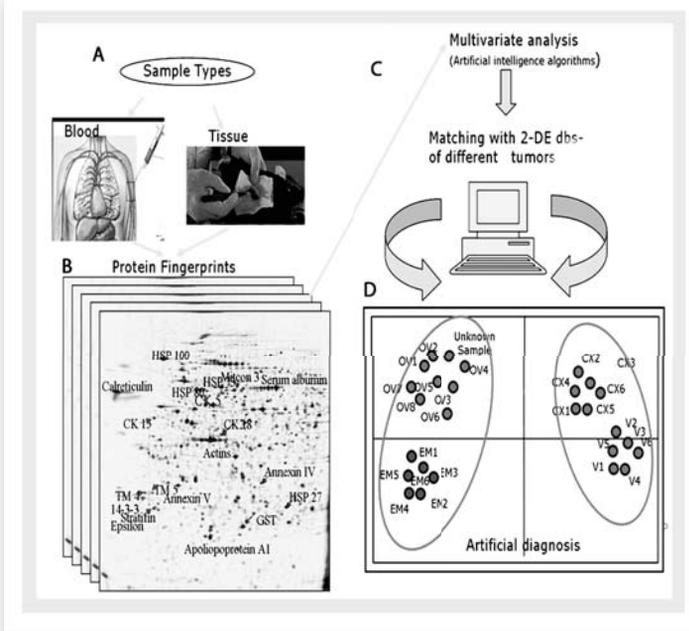


Figure 3: Schematic illustration of novel way of artificial tumor classification using multivariate data analysis of differentially expressed proteins. (A) Tissue or blood sample is processed, (B) Protein fingerprint is generated by 2-DE, (C) Fingerprint images are deposited in tumor database for expression analysis, (D) Computer assisted image analysis for artificial tumor classification.

Project Title: Evaluation of Anti-Tumor Activity of $\gamma\delta$ T-cells in Cancer Patients, RAC # 2030 022.

Investigators: Mahmoud Al-Jurf, Khaled Al-Hussein, Abdelghani Tbakhi, Hamad Al-Omar, Adher Al-Sayed and Ameera Gaafar

PROJECT DESCRIPTION

$\gamma\delta$ T-cells play an important role in innate and adaptive

anti-tumor immunity. The task of innate effectors cells such as macrophages, NK cells, NKT-cells, and $\gamma\delta$ T-cells in tumor immuno-surveillance and tumor immunotherapy has recently been revisited. T-cells bearing the TCR $\gamma\delta$ represent a minor subset of human peripheral T-cells (1-10%), differing from $\alpha\beta$ T-cells in cell surface phenotype. Their distribution and function in humans is less well characterized, though some evidence has been gathered indicating that $\gamma\delta$ T-cells have been shown to exhibit major histocompatibility complex (MHC)-unrestricted cytotoxicity against some tumors. In addition, it has been recognized that donor-derived $\gamma\delta$ T-cell may serve as facilitating cells, promoting the engraftment of donor hematopoietic stem cells across varying degrees of MHC disparity. And yet, the in-depth position of $\gamma\delta$ T-cells in the immune response of tumor patients remains largely elusive and controversial. 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.

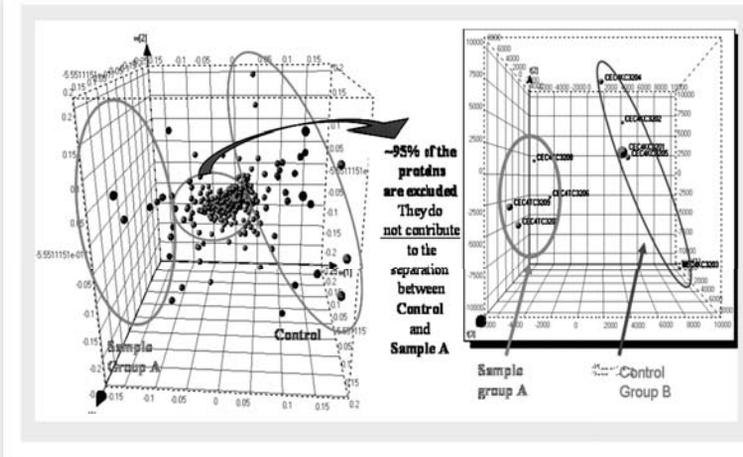


Figure 4: Figure2. Data mining: Selection of significantly differentially expressed proteins that will be used for Molecular Classification of Tumors using Multivariate Analysis of Protein Expression Profiles.

PROGRESS MAJOR FINDINGS

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.

a) $\gamma\delta$ T-cells were screened for the known granzyme B gene polymorphism in the breast cancer and

normal controls. This study is completed and currently a manuscript is considered for publication by the journal of

Experimental Hematology with major revision. An abstract is published in Exp.Hematol. and a final report is submitted and accepted by ORA.

b) Production and genetic mutation of perforin produced by $\gamma\delta$ T-cells might contribute to the pathology and disease outcome of breast cancer patients. Currently we screened 66 normal and 10 breast cancer Saudi female donors. Data is being analyzed.

Project Title: Identification of HLA Alleles in Normal Saudi Individuals by Sequence Based Typing, RAC # 2010-002.

Investigators: Khaled Al-Hussein and Abdelghani Tbakhi

PROJECT DESCRIPTION

The major histocompatibility complex (MHC) also referred to as Human Leukocytes Antigens (HLA)

has been linked to the development of most autoimmune diseases, cancer, susceptibility to infectious agents and most importantly allograft rejection. Until recently, much of what is known regarding the population genetics of HLA in Saudi Arabia has been derived from the application of conventional methods and the alleles identified in Northern European and North American populations. The frequencies of HLA alleles however, vary considerably among different ethnic groups. The conventional techniques used by most laboratories, including those in Saudi Arabia, for HLA tissue typing are incapable of detecting all allelic variations with precision without information on their DNA sequences.

PROGRESS

In this KACST approved project, 1000 healthy Saudi individuals, from various regions of the Kingdom of Saudi Arabia, was typed from their HLA allele using a valuable method known as Sequence Based Typing (SBT) whereby a spectrum of HLA Class I and II alleles was identified. This will facilitate the establishment of a Saudi HLA allele database. We have studied the frequency of HLA Class I (-A, -B, -C) alleles in 1000 normal Saudi individuals. Twenty-one HLA-A alleles were detected. HLA-A*0231 and HLA-A*3102/3104-5 were found to be the most frequent and the most diversified region in the HLA-Class I loci is the HLA-C. Twenty-eight HLA-C alleles were detected.

Project Title: HLA Gene association in Patients With Type 1 Diabetes in Saudi Arabia, RAC # 2000 029

Investigators: Khaled Al-Hussein and Mohammed Al-Ahmed

PROJECT DESCRIPTION, PROGRESS AND MAJOR FINDINGS

Type 1 diabetes is an autoimmune disease caused by a combination of genetic, immunological and environmental factors. It is mediated by both CD4+ and CD8+ T-cells and result in the destruction of beta islet cells in the pancreas. Since T-cells see the antigen in the context of the MHC-antigen complex,

immunogenetic studies are imperative to decipher the interaction of both humoral and cellular mediated interaction in the auto-destruction of beta islet cells. Previously (HLA) class II DQB1*0201/0202-DRB1*04 genotype was reported to be a predisposing allele to type 1 diabetes {insulin-dependent diabetes mellitus (IDDM)} in the Saudi Arabian population, whereas significant protection was found to be conferred by DPB1*0401. Our reported data showed that high frequency of the DPB1*0104 allele, even in the presence of predisposing DQB1*2 allele, in healthy subjects may indicate a protective effect of this combination of HLA alleles against type 1 diabetes. In this project we used a larger cohort of control subjects and patients to confirm the above mentioned hypothesis that protective HLA class II genes can override the risk provided by HLA-DQ susceptibility alleles.

Project Title: Study of the Relationship Between the Genetic Polymorphisms of the Natural Killer Cell Receptor (KIR) Genes and the Outcome of the Hematopoietic Stem Cell Transplantation for Hematological Malignancies in Saudi Arabia, RAC # 2051001 (KACST: AT-26-03).

Investigators: Mahamoud Al-Jurf, Abdelghani Tbakhi, Ameera Gaafar Mohamed and Khaled Al-Hussein

PROJECT DESCRIPTION

Natural killer (NK) cells can mediate the acute rejection of bone marrow cell (BMC) allografts. The mechanisms underlying the rejection process remain unclear. NK cells express 1) inhibitory receptors specific for major histocompatibility complex (MHC) class I molecules and 2) activating receptors with diverse specificities. Inhibitory NK receptors confer to NK cells the ability to discriminate between MHC class I positive and negative target cells. Therefore they are involved in the control of NK cell tolerance to self and the elimination of cells that have down regulation of MHC class I molecules. Neither the KIR gene locus polymorphism nor the degree of KIR mismatch of our HLA donor-recipient transplant pairs has

been identified in the Saudi population. Therefore, a prospective study that focuses on these two main aims is warranted. The purpose of this study is to investigate the effects of KIR incompatibilities in HLA- matched related donor-recipient pairs.

PROGRESS

To date 60 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: 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, Abdelgani Tbakhi, Ameer Gaafar and Khaled Al-Hussein

PROJECT DESCRIPTION

Transplantation is the ideal therapy for the majority of end-stage organ diseases. Organ transplantation, in Saudi Arabia, is a well-established modality in the treatment of organ failure. Genotyping profiles of the Natural killer cell

Immunoglobulin-like receptors (KIR) have been reported to vary among different ethnic groups. This report represents a novel longitudinal study to investigate the underlying immune system genes, which contribute to graft survival or rejection in the Saudi population. New molecular markers will also be identified to predict the presence or absence of detrimental factors that underlay immune responses in clinical transplantation.

PROGRESS

Genotyping profiles of the Natural killer cell Immunoglobulin-like receptors (KIR) have been reported to vary among different ethnic groups. We commenced a longitudinal study for the first time, to investigate the underlying immune system genes, which might contribute to the graft survival or rejection in Saudi population. We intended to identify new molecular markers in order to predict the presence or absence of detrimental factors underlying all immune responses in clinical transplantation. In addition, our main objective is to compare KIR distribution between kidney transplant donors and recipients.

MAJOR FINDINGS

Similar to most published data, we observed the dominance of the two framework genes 3DL2 and 3DL3 which are present in all (100%) recipients and donors investigated so far. While the other KIR genes vary in their frequencies. We also observed the predominance of AA1 genotype. Allograft rejection was observed in 14 (19%) recipients. No association was observed of KIR genotypes with rejected or stable graft. In addition, a polymerase chain reaction with sequence-specific primers was used to screen for the known cytokines SNPs within genes encoding IFN- γ , TGF- β , TNF- α , IL-6 and IL-10 in the same set of donors/ recipients' pairs mentioned above. We observed that low IL-10 productivity is positively correlated with stable graft. The project is progressing very well and almost 90% of its aims were fulfilled. Currently data is analyzed and a manuscript in preparation.

PUBLICATIONS

- ↪ Paolo Fiorina, Mollie Jurewicz, Andrea Augello, Andrea Vergani, Shirine Dada, Stefano La Rosa, Martin Selig, Jonathan Godwin, Kenneth Law, Claudia Placidi, R. Neal Smith, Carlo Capella, Scott Rodig, Chaker N. Adra, Mark Atkinson, Mohamed H. Sayegh and Reza Abdi, "Immunomodulatory function of bone marrow-derived mesenchymal stem cells in experimental autoimmune type 1 diabetes". *The Journal of Immunology*, 2009, 183, 993-1004.
- ↪ Iqniebi A, Al-Suliman, Gaafar A, Mohamed G., Al Hussein K, Tabbara K. "HLA-DRB1 Among Patients with Vogt-Koyanagi-Harada Disease in Saudi Arabia". (Submitted to *Human Immunology*) 2009.
- ↪ Gaafar A, Sheereen A, Iqniebi A, Al-Suliman A., Mohamed G., Al-Hussein K. "Killer cell immunoglobulin – like receptor gene diversity in Saudis". (Submitted to *Tissue Antigens*) 2009.
- ↪ 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" (Accepted, *Experimental Hematology*) 2009.
- ↪ Stig Linder & Ayodele Alaiya, "Serum Efficacy Biomarkers for Oncology, Biomarkers in Medicine", February 2009, Vol. 3, No. 1, Pages 47-54.
- ↪ Abdi R, Fiorina P, Adra CN, Atkinson M, Sayegh MH. "Immunomodulation by Mesenchymal Stem Cells": A Potential Therapeutic Strategy for Type 1 Diabetes Mellitus." 57: 1759-1767, *Diabetes*, July 2008.
- ↪ Lehe C, Ghebeh H, Al-Sulaiman A, Al Qudaihi G, Al-Hussein K, Almohareb F, Chaudhri N, Alsharif F, Al-Zahrani H, Tbakhi A, Aljurf M, Dermime S. "The Wilms' tumor antigen is a novel target for human CD4+ regulatory T-cells": implications for immunotherapy : *Cancer Res.* 2008 ;68 (15): 6350-9.
- ↪ 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.* 2008, (2):123-32.
- ↪ Hawsawi NM, Ghebeh H, Hendrayani SF, Tulbah A, Al-Eid M, Al-Tweigeri T, Ajarim D, Alaiya A, Dermime S, Aboussekhra A. "Breast carcinoma-associated fibroblasts and their counterparts display specific changes". *Cancer Res.* 2008 Apr 15; 68(8):2717-25.
- ↪ Roblick UJ, Bader FG, Lenander C, Hellman U, Zimmermann K, Becker S, Ost A, Alaiya A, Bruch HP, Keller R, Mirow L, Franzén B, Ried T, Auer G, Habermann JK. "Undifferentiated pelvic adenocarcinomas: diagnostic potential of protein profiling and multivariate analysis". *Int J Colorectal Dis* 2008 May; 23(5):483-91.
- ↪ "Chronic Myeloid Leukemia Global Opinion Leader Summit (CML GOLS)", Athens, Greece on 2 – 4 March 2007.
- ↪ 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.
- ↪ 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.
- ↪ 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.

ABSTRACTS

- ↪ Andrew Wetzig, Mary Angeline Esperas, Imaduddin Kanaan, Chaker Adra. "Adult Olfactory Mucosa: A Source of Mesenchymal and Neural Stem Cells for Spinal Cord Repair? Accepted for oral presentation, 2008 KFSH&RC Annual Research Report, 16-18 March 2009, Research Centre.

-
- ↪ Hazem Ghebeh, Layla Al-Mansouri, Ghida Sleiman, Jasminka Godovac-Zimmermann, Ayodele Alaiya, and Chaker Adra. "Identification of a stem cell enriched population in normal and cancer breast tissues". Accepted for oral presentation, 2008 KFSH&RC Annual Research Report, 16-18 March 2009, Research Centre.
 - ↪ Khaldoun Al-Romaih, Saleh Al-Othman, Hamad Al-Mojalli, Hadeel Al-Manea, Noura Atallah, Mai Al-Mohanna, Martin Pollak and Chaker Adra. "Genetic Basis of Kidney Disease; The Path Towards Accurate Diagnosis". Accepted for oral presentation, 2008 KFSH&RC Annual Research Report, 16-18 March 2009, Research Centre.
 - ↪ Monther Al-Alwan, Safiah Olabi, Hazem Ghebeh, Eman Barhoush, Asma Tulbah, Taher Tweigeri, Dahish Ajarim, Chaker Adra. "Fascin regulate breast cancer metastasis via up-regulated secretion of Matrix Metalloprotease and suppression of Breast Cancer Metastasis Suppressor 1". Accepted for oral presentation, 2008 KFSH&RC Annual Research Report, 16-18 March 2009, Research Centre.
 - ↪ Fadia El Bitar, Muna Negash, Yvette Akwa, Chaker Adra. "Pregnenolone sulfate: Neuroactive steroid that provides neuroprotection against *in vitro* β -amyloid peptide-induced neurotoxicity". Accepted for oral presentation, 2008 KFSH&RC Annual Research Report, 16-18 March 2009, Research Centre.
 - ↪ Ameera Gaafar, Atia Sheereen, Alia Iqneibi, Abdullah Al-Sulaiman, Khalid Al-Hussein. "Killer cell immunoglobulin – like receptor genes diversity in Saudi population". Accepted for poster presentation, 2008 KFSH&RC Annual Research Report, 16-18 March 2009, Research Centre.
 - ↪ Mai Al-Mohanna, Muhammad Aslam, Zakia Shinwari, Maha Rodayan, Maha Al-Eid, Layla Al-Mansouri, Irfan Ahmad, Kamal Hanash, Chaker Adra, Ali Bin Mahfooz, and Ayodele Alaiya. "Identification of Proteins Involved in Benign and Malignant Prostate Tumors". Accepted for poster presentation, 2008 KFSH&RC Annual Research Report, 16-18 March 2009, Research Centre.
 - ↪ Mai Al-Mohanna, Zakia Shinwari, Maha Rodayan, Maha Al-Eid, Falah Al-Mohanna, Raafat El-Sayed, Chaker Adra and Ayodele A. Alaiya. "Protein Expression Changes during Tumor Response to Therapy: Identification of leakage proteins from tumor tissue in peripheral blood". Accepted for poster presentation, 2008 KFSH&RC Annual Research Report, 16-18 March 2009, Research Centre.
 - ↪ Mai Al Mohanna, Zakia Shinwari, Tarek Owaidah, Maha Al-Rodayan, Fahad Al Mohareb, Fahad Al Sharif, Randa Al Nounou, Chaker Adra, Naeem Chaudhri, Mahmoud Al Jurf and Ayodele Alaiya. "Molecular Classification of Bone Marrow Failure Syndrome: Analysis of Protein Expression Patterns between Aplastic Anemia, Hypoplastic Myelodysplastic Syndrome and Paroxysmal Nocturnal Hemoglobinuria". Accepted for oral presentation, 2008 KFSH&RC Annual Research Report, 16-18 March 2009, Research Centre.
 - ↪ Khaldoun Al-Romaih, Saleh Al-Othman, Mai Al-Mohanna, Hamad Al-Mojalli, Hadeel Al-Manea, Martin Pollak and Chaker Adra. "Genetic Basis of Glomerular Disease in The Middle East", Accepted for poster presentation, 2nd KFSH&RC Residents' Research Day, 21 January 2009, Research Centre.
 - ↪ Maha Al-Mozaini, Mona Nagashi, Sahar Al-Thawadi, Sami Al-Hajjar, Chaker Adra and Mohammed Al-Ahdal. "Detection of mutations within the ul97 gene of ganciclovir resistant cytomegalovirus in clinical isolates". Accepted Abstract for oral presentation, 2nd KFSH&RC Resident's Research Day, 21 January 2009, Research Centre.
 - ↪ Hazem Ghebeh, Cynthia Lehe, Eman Barhoush, Pulicat Manogaran, Ayodele Alaiya, Taher Al-Tweigeri, Abdelilah Aboussekhra, and Said Dermime, "Doxorubicin selectively and significantly decreases the surface expression of B7-H1 in breast cancer cells". Accepted for oral presentation, 2nd KFSH&RC Residents' Research Day, 21 January 2009, Research Centre.
 - ↪ Maha Al-Mozaini, Mona Nagashi, Asma Tulbah and Mohammed Al-Ahdal. "A73 gene in nasopharyngeal carcinoma and its oncogeneic potential". Accepted for poster presentation, 2nd KFSH&RC Residents' Research Day, 21 January 2009, Research Centre.

-
- ↪ Maha Al-Mozaini, Gustavo Bodelon, Claudio Elgueta Karstegl, Boquan Jin, Mohammed Al-Ahdal and Paul J. Farrell. "Epstein-Barr Virus Bart Gene Expression". Accepted for oral presentation, 2nd KFSH&RC Residents' Research Day, 21 January 2009, Research Centre.
 - ↪ Maha Al-Mozaini, Khalid Al-Mashari, Mohammed Al-Ahdal, Chaker Adra and Jay Fishman. "Post Transplant Lymphoproliferative Disorder in Miniature Swine: A Unique Model for Studies of Human Disease". Accepted for poster presentation, 2nd KFSH&RC Residents' Research Day, 21 January 2009, Research Centre.
 - ↪ Abdullah Al-Dhfyhan, Maha A. Al-Mozaini, Tarek Aboufadel and Chaker N. Adra. "Chemical Synthesis and Biological Evaluation of Compound AT-4 as A Novel and Selective Antimitotic Agent, with Direct Inhibitory Effect on Onco Protein Cyclin B1". Accepted for oral presentation, 2nd KFSH&RC Residents' Research Day, 21 January 2009, Research Centre.
 - ↪ Andrew Wetzig, Mary Angeline Esperas, Ayodele Alaiya, Imaduddin Kanaan, Chaker Adra. "The Propagation of Mesenchymal and Neural Stem Cells from Adult Olfactory Mucosa" Accepted for oral presentation, 2nd KFSH&RC Residents' Research Day, 21 January 2009, Research Centre.
 - ↪ Ayodele A. Alaiya and Mai Al-Mohanna. "Molecular Classification Of Human Cancers Using Analysis Of Protein Expression Profiles". 1st International Conference On Biotechnology (Icob) Center Of Excellence In Biotechnology Research King Fahad Cultural Center, Riyadh, Saudi Arabia 16-18 February 2009 (Poster). Abstract Published in Conference Abstract Book.
 - ↪ Ghebeh H, Lehe C, Barhoush E, Pulicat M, Alaiya A, Al-Tweigeri T, Aboussekhra A, Dermime S. Doxorubicin selectively and significantly decreases the surface expression of B7-H1 in breast cancer cells Presented International Society for Biological Therapy of Cancer meeting held 16-19 March 2008, San Diego, CA, USA, published in *J Immunother* 2008.
 - ↪ Al-Alwan MM, Ghebeh H, Barhoush E, Tulbah A, Tweigeri T, Ajarim D, Alaiya A, Aljurf M, Dermime S. Direct correlation between fascin expression and breast cancer metastasis. *Advance in Cancer Research: From Laboratory to the Clinic*, Dead Sea, Jordan (March 2008).
 - ↪ Al-Qudaihi G., Lehe C., Negash M., Al-Alwan M., Ghebeh H., Mohamed S., Saleh A.J. M., Dickson A., Aljurf M., Dermime S., CD8+ cytotoxic T lymphocytes generated against a WT1 peptide analog enhance the lytic activity of leukemic cells". (Poster) 20th Meeting of the European Association for Cancer Research, Lyon, France 5-8 July 2008.
 - ↪ 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.
 - ↪ Gaafar A, Al-Omar HM, Almkhlaifi 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.
 - ↪ 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. "Application of Free Flow Electrophoresis (FFE) for proteomic analysis of plasma, serum and bone marrow of Chronic Myeloid Leukemia and Aplastic Anemia patients", HUPO, 6th 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*.

THE RESEARCH CENTRE
TRAINING & EDUCATION OFFICE

The Research Centre Training & Education Office

The Research Centre Training and Education Committee (RCTEC) was formed to formulate guidelines & procedures in providing and administering the training and education activities in the Research Centre. RCTEC oversee the RCTEO which facilitates In-House Training in progressive fields of science and technology, In-Kingdom and Out-Kingdom training and education leading to higher education, it support students to prominent institutions to certify with the advancement of technology, and RC-TEO organizes and conducts special courses and workshops throughout the year.

EXPERTISE

The RCTEO facilitates external training and education for Saudi citizens who wish to pursue MSc, PhD degrees and Postdoctoral Fellowship. Affiliations with reputable scientific and educational local and international institutions have been established to ensure that the latest technology is acquired hence, career development is advanced.

Director:

Refaat Al-Mazrou, MSc, MIPEM

Committee Members:

Ayodele Alaiya, MD, PhD

Anas Alazami, DPhil

Abdalla Al-Haj, PhD

Ibrahim Al-Jammaz, PhD

Ahmed Al-Qahtani, PhD

Yasmin Al-Twajiri, PhD

Ali Al-Odaib, PhD

Sahal Al-Hajj, PhD

Huda Al-Mosallam

Administrative Staff:

Huda Al-Mosallam - Manager

Abdulrahman Al-Lahoo - Coordinator

Faten Al-Khateeb - Coordinator

Gina Rodil - Secretary

Jamila Fernandez - Secretary

Arwa Fayyad – Bilingual Secretary

Sara Abu Raad – Bilingual Secretary

ACTIVITIES

The Research Centre Training and Education Committee and its office administer the following programs:

POSTDOCTORAL FELLOWSHIP PROGRAM (PDFP)

This is a program of study and research training at an institution abroad for the Research Centre employees. The Fellowship maximum duration of two years, should be relevant to the employees' work and the future directions of the Research Centre. This program is under the Hospital Scholarship guidelines.

Program	On-Board	Completed
PhD Fellowship	0	0

HOSPITAL SCHOLARSHIP PROGRAM (HSP)

The Institution helps qualified employees to pursue their studies and obtain a higher degree or gain practical experience in their field, to serve the needs of KFSH&RC. The primary objective of this program is to raise the overall educational and healthcare standards at KFSH&RC by encouraging employees to develop their academic and technical skills. The scholarship can be given either as Out-of-Kingdom Study Program or In-Kingdom Study Program.

Program	On-Board	Completed
PhD	17	3
MSc	5	3

IN-HOUSE RESEARCH GRADUATE FOR NON-RC EMPLOYEES PROGRAM (I-HGP)

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.

Program	On-Board	Completed
PhD	5	1
MSc	7	2

GRADUATE ASSISTANTSHIP PROGRAM (GAP)

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 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 skills through various scholarship programs. Such disciplines can be offered to eligible candidates to pursue their research studies abroad or at the KFSH&RC in collaboration with recognized international universities and institutes.

Program	On-Board	Completed
PhD	4	0
MSc	3	0

IN-HOUSE TRAINING PROGRAM (I-HTP)

The Research Centre provides training opportunities for eligible candidates from other institutions for a maximum of six (6) months. These include:

- Undergraduate students who are seeking training related to their university degree
- Individuals who are seeking training to enhance their qualifications
- Saudi citizens employees in public and private sectors who want to develop an aptitude for research
- Recipients of fellowships sponsored by international institutions such as the International Atomic Energy Agency (IAEA) seeking on-the-job training
- Medical Fellows/Residents for training in Research Methodology

- High School students interested in a career in Biomedical Sciences can be given a short orientation

Program	On-Board	Completed
In-House Training	109	104

FUTURE SCIENTISTS PROGRAM (FSP)

The aim of this program are to assist talented young male high school Saudi nationals in the acquisition of scientific skills, to help them appreciate science and its value to humanity, and to prepare them for a future in the field of Biomedical Sciences by providing an environment for their scientific growth.

Program	Completed
FSP	14

IBN SENA PROGRAM (ISP)

An agreement was created in 2006 between KFSH&RC-Research Centre and King Abdulaziz and his Companion for Giftedness & Creativity Foundation to assist talented young Saudi nationals to integrate their scientific skills/talents in preparing them in different areas of Science in the future.

Program	Completed
FSP	18

SUMMER TRAINING PROGRAM (STP)

The RC-TEO encourages cooperation with national institutes for the exchange of information and pursuit of knowledge in an organized and productive manner. The objective of this program is to expose the undergraduate students to the work environment and give them the chance to get hands-on training in the

basic science and to give them the chance to show their abilities and find out their suitable field of science in the future.

Program	Completed
STP	22

RESEARCH CENTER SEMINAR (RCS)

RCTEC represented by its office, organizes a weekly seminar to be given by Research Center scientists. Special seminars also take place from time to time in the Research Center through the close collaboration between the Office and the concerned departments.

Program	Completed
RCS	44

WORKSHOP AND CONFERENCES (WS&CONF)

The Research Centre Training and Education Office assists in organizing a number of annual workshops, conferences and special courses/events in specific field of science.

Program	Completed
WS&Conf	12

OTHER RESPONSIBILITIES

RCTEC processes and ensures that all necessary guidelines are applied to the following leave categories:

- Business Leave (BL)
- Professional Leave (PL)
- Educational Leave (EL)

THE MEDICAL AND
CLINICAL OPERATIONS
REPORT

This page was left intentionally blank.

THE DEPARTMENT OF
DENTISTRY

The Department of Dentistry

ENDODONTICS RESEARCH ACTIVITIES

Project Title: Outcome of Endodontic Treatment in Organ Transplant Patients, RAC # 2071033.

Primary Investigator: Dr Abdulrahman Al Dawood

Co-Investigators: Dr Tariq Al Ali and Dr Mats Eckerbom

Chairman:

Abdulhadi Abanmy, BDS, DMSc

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 METHODS

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 out come 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.

PEDIATRIC DENTISTRY RESEARCH ACTIVITIES

Project Title: Pattern of Cleft Lip and Palate in Hospital-Based Population in Saudi Arabia, RAC# 991030.

Investigators: Dr Aziza Al-Johar, Dr Kandasamy Ravichandran and Ms Shazia Subhani

ABSTRACT

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 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*, November 2008, Vol 45, No. 6: 592-596.

PROSTHODONTICS RESEARCH ACTIVITIES

Project Title: Rare Dental Disorder Registry, RAC#2071082.

Primary Investigator: Dr Adeeb Al Omrani

Co-Investigators: Dr Hans Hansson, Dr Richard Hakansson, Dr Khalid Al Zoman and Ms Shazia Naz Subhani

PROJECT DESCRIPTION

Congenital Oral Anomalies are a broad category of health conditions that are present at birth and are a deviation from normal anatomic growth, development, or function. There is an urgent need to increase knowledge about oral rehabilitation for people with oral/dental disabilities and new methods for treatment must be developed and evaluated. 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.

Project Title: Gene Expression & Immunohistological findings in patients With Papillon Lefèvre 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 and Christer Ullbro, DDS, PhD

Research Investigators: Namik Kaya, PhD (Co-PI), Dilek Colak, PhD, Said Dermime, PhD and Hazem Ghebeh, PhD

PROJECT DESCRIPTION

Papillon-Lefebvre syndrome is an autosomal recessive disorder characterized by hyperkeratosis of palm and soles and by a generalized aggressive periodontitis and premature loss of primary and permanent dentition. It is relatively prevalent in a small village north of Riyadh with more than 60 patients being followed in the dental clinic at KFSH&RC. Severe periodontal disease plays an important role in PLS

resulting in premature loss of primary and permanent dentition. Two mutations have been identified in the cathepsin C (CTSC) gene in this population. The aim is to study the histopathology, immunological profile, and gene expression of PLS from blood samples and gingival biopsies; and thus shed more light on the pathophysiology of the disease and explore whether new subclasses of this disease can be identified based on gene expression profiles. Furthermore, we aim to establish a preventative program among this high-risk group through carrier testing and genetic counseling. The study will include 40 PLS patients presented at the dental department in KFSH&RC, retrospectively. A correlation may be found between the immunological status/gene expression and level/severity of periodontal infection. This may give more insight on the role of cathepsin C in the disease.

AIMS

Our aim in this study is to perform a thorough genetic and immunological evaluation in a cohort of Saudi patients with PLS from the following aspects:

- Comprehensive genetic assessment:
 - ↪ Gene expression profiling of PLS patients, carriers and controls in the blood and patients, and controls in gingival tissue.
- Study the immunologic status of PLS from blood samples:
 - ↪ Detailed neutrophils function including: adhesion (by means of CD11/CD18 expression) chemo taxis, phagocytosis and killing abilities (by evaluating the oxidative burst function).
 - ↪ Lymphocytes phenotypic distribution, and lymphocytes proliferation assays.
 - ↪ Natural Killer cytotoxic activity.

THE ONCOLOGY CENTRE

The Oncology Centre

KFSH&RC enjoys the recognition of having the largest cancer facility in the Gulf region where more than 3,000 patients are treated annually. Established with a mission of providing excellent cancer treatment, education and research, the Oncology Centre evolved over the years towards its vision of becoming one of the best international centres for cancer research, prevention, and treatment. Accredited by the World Health Organization (WHO) as a Collaborating Centre for Cancer Prevention and Control, cancer patients are assessed in multidisciplinary clinics and provided with treatment in accordance with disease specific internationally accepted management guidelines. Our oncologists continue to actively address national oncology problems through their involvement in institutional, national, and international research protocols with the invaluable support of the Centre's Research Unit which also serves as a hospital base for cancer and bone marrow transplantation registries. Major achievements for the year include:

- Inaugural publication of the KFSHRC Hematology/Oncology and Stem Cell Therapy Journal in January 2008.
- Awarded membership to the CBMTG (Canadian Bone Marrow Transplantation Group) and the EBMT Clinical Trials Group (EBMTG). First trial approved.
- Achieved institutional membership and collaborative studies with Southwest Oncology Group (SWOG) and the American College of Radiology Imaging Network (ACRIN).
- Eastern Mediterranean Blood & Marrow Transplantation) Group EMBMT established. Phase I completed, Phase II in progress. First article published in *Bone Marrow Transplantation Journal*.
- Three collaborative studies started with RTOG on glioblastoma, brain and cervical cancer.
- Twelve new research studies started; five studies completed.

Director:

Dahish Ajarim, MD

Deputy Director:

Mahmoud Aljurf, MD

- Four disease specific database/registries opened for rectal cancer, Hodgkin's, Non-Hodgkin's and lymphoma.
- Five clinical protocols established in epithelial ovarian cancer, breast cancer, renal cell carcinoma, and myeloid leukemia.

FUTURE RESEARCH DIRECTION

- Promote well designed clinical/transitional research activities.
- Establish firm collaboration and team work with Research Center and other related organizations to promote translational research.
- Establish membership and collaboration with national, regional and international clinical research cooperative groups.
- Expand and maximize utilization of available database for certain tumor sites in research direction and bench marking.
- Establish refresher courses for Clinical Research Coordinators to achieve CCRP certification.
- Establish more international multi-centre clinical research trials in collaboration with international cooperative groups like RTOG, SWOG, ECOG, CBMTG, EBMT and ACRIN to answer important scientific questions.
- To host international symposia with emphasis on clinical research.
- To conduct more pioneering scientific research to advance cancer treatment and care.
- To work with the latest and emerging technology with an end to providing the most advanced treatments, including therapies and drugs available only through clinical trials at KFSH&RC.

RESEARCH PROJECTS

Project Title: Cultural and Family Influence in Decision Making and Other Social Issues in Arab Society Among Patients Undergoing High Dose Chemotherapy and Autologous Stem Cell Transplant: Cultural Adapted FACT-BMT Study,, RAC# 2071-079.

Investigators: S Akhtar, A Al-Zahrani, . Abdalla, E Colcol, H Soudy and I Maghfoor

Background: in Arab culture, family and cultural influence in decision making for high dose chemotherapy and autologous stem cell transplant (HDC-ASCT) and subsequent care / issues for a patient is not well studied.

Method: We translated into Arabic the “Functional Assessment of Cancer Therapy –Bone Marrow Transplant” (FACT-BMT) quality of life questionnaire. We also developed 17 culturally adapted questions (Cultural Adapted FACT-BMT) for relevant cultural issues.

Results: Sixty patients who had HDC ASCT for non Hodgkin’s lymphoma and Hodgkin’s lymphoma participated. Males 39 (65%), females 21 (35%). Median age 32 years (15 -62 years). Eighty-two percent of family members were aware of the patient’s condition and treatment. During HDC ASCT decision making, 45% patients made the decision by themselves, patients + other family member/s in 43%, 12%, family member/s only and treating physician + patient + the family in 13% cases. More than 85% patients had unchanged relationship with family members. Problems getting married due to this condition in 33% of applicable patients. 20% patients were concerned about their ability to have children. Education was effected in 50% of applicable patients. Use of alternative treatment was 77%; honey 72%, black seeds (habbat albarakah) in 60%, Zam Zam 62%, camel milk and camel urine alone or combined together in 23%. 60% patients had counseling by Sheikh.

Conclusion: This study provided important information. This can be used to improve education and support for specific group of patients undergoing HDC ASCT. This can also be used to provide better culturally adaptive supportive strategies.

DATABASE

Project Title: Establishment of Acute Lymphocytic Leukemia Data Base in the Department of Oncology, RAC#2021-051.

Investigators: Chaudhri N, Aljurf M, Al-Sharif F, Mohareb F and Zahrani H

PROJECT DESCRIPTION

Database.

PROGRESS

Active.

Project Title: Establishing a Data Base for Aplastic Anemia and Other Marrow Failure Syndrome, RAC#2021-084.

Investigator: Al-Zahrani H

PROJECT DESCRIPTION

Database.

PROGRESS

Active.

Project Title: Sarcoma Database((RAC#2081-015.

Investigators: Memon M, Hussein S and Colcol E

PROJECT DESCRIPTION

Database.

PROGRESS

Active.

Project Title: Prospective Data Collection of Newly Diagnosed Hodgkin’s Disease and Non-Hodgkin’s Lymphoma Cases, RAC#(RAC#2021-048.

Investigator: Akhtar S

PROJECT DESCRIPTION

Database.

PROGRESS

Active.

Project Title: Retrospective Database for Lymphoma patients infected With Hepatitis B Virus/Hepatitis C Virus who received Cytotoxic Chemotherapy: Outcome, Incidence of Hepatitis Reactivation, Identification of Risk Factor and Duration of Lamivudine Prophylaxis for Prevention of HBV Reactivation, RAC#2071-072.

Investigator: Al-Zahrani A

PROJECT DESCRIPTION

Database.

PROGRESS

Active.

Project Title: Nasopharyngeal Carcinoma Database, RAC#2051-017.

Investigator: Al-Rajhi N

PROJECT DESCRIPTION

Database.

PROGRESS

Active.

Project Title: Data Collection of Newly Diagnosed Breast Cancer Cases (2001-2006), RAC#2051 29.

Investigators: Ajarim D, Twegieri T, Ezzat A, Alsayed A, Al-Shabanah M and Al-Malik O

PROJECT DESCRIPTION

Database.

PROGRESS

Active.

Project Title: Prospective Database for Acute Myeloblastic Leukemia, RAC#2051-057.

Investigator: Chaudhri N

PROJECT DESCRIPTION

Database.

PROGRESS

Active.

Project Title: Prospective Database for Chronic Myelogenous Leukemia, RAC#2051-056.

Investigator: Chaudhri N

PROJECT DESCRIPTION

Database.

PROGRESS

Active.

Project Title: Data Collection of Newly Diagnosed Breast Cancer Cases (2007 onwards), RAC#2051-029.

Investigator: Ajarim D

PROJECT DESCRIPTION

Database.

PROGRESS

Active.

PROTOCOL

Project Title: A SU011248 Expanded Access Protocol for Systemic 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 and Abdelsalam M

PROJECT DESCRIPTION

Protocol.

PROGRESS

Active.

Project Title: Phase II Trial of Neo-Adjuvant (FEC100) / Cisplatin-Docetaxel + Trastuzumab in Women Who Overexpressed or Amplified Her2/Neu With Locally Advanced Breast Cancer, RAC#2061-048.

Investigators: Twegieri T, Ajarim D, Ezzat A, Alsayed A, Al-Shabanah M, Hussek M, Al-Malik O, Tulbah A, Pant R, Shahid M, El-Eissawy M, El-Kum N, Retuta R and Fatani D

PROJECT DESCRIPTION
Protocol.

PROGRESS
Active.

Project Title: Cytogenetic Analysis of Bone Marrow Specimens Prior to High Dose Chemotherapy (HDC) and Autologous Stem Cell Transplant (ASCT) in Patients With Non Hodgkins Lymphoma (NHL) and Hodgkins Lymphoma (HD), RAC#2041015.

Investigators: Akhtar S, Iqbal A, El-Weshi A, Bazarbashi S, Ajarim D and Maghfoor I

PROJECT DESCRIPTION
Protocol.

PROGRESS
Active.

Project Title: Autologous Peripheral Blood Stem Cell Transplantation With *In Vivo* Purging As An Alternate Stem Cell Transplantation Program For Patients With Acute Myelogenous Leukemia (Aml) In First (Cr1) And Second (Cr2) Complete Remission With No Hla Matched Related Donor, RAC#2001 044.

Investigators: Al-Mohareb F, Gyger M, Chaudhri N, Al-Zahrani H, Al-Sharif F, Sahovic E, Aljurf M, Al-Omar H, Roberts G, Nounou R, Tbakhi A, Iqbal A, Aslam A, Seth P, Al-Zahrani H, Al-Quarshi F, Zaidi S, Morshed M, Colcol E, Chadhary A and Belkhedim R

PROJECT DESCRIPTION
Protocol.

PROGRESS
Active.

Project Title: Induction of Mixed Hematopoietic Chimerism in Patients Using Fludarabine, Low Dose TBI, PBSC Infusion and Post Transplant Immunosuppression With Cyclosporin and Mycophenolate, RAC#2001 044.

Investigator: Al-Jurf M

PROJECT DESCRIPTION
Protocol.

PROGRESS
Active.

Project Title: Functional Assessment of Cancer Therapy - Bone Marrow Transplant (FACT-BMT), RAC#2071-079.

Investigators: Al-Zahrani A, Akhtar S, Hussein S, Eltayb M, and Colcol E

PROJECT DESCRIPTION
Protocol.

PROGRESS
Active.

Project Title: A Pilot Trial of Pre-Operative Chemoradiotherapy Using Capecitabine (Xeloda), External Beam Radiation and Cetuximab (Erbiximab) Followed by Definitive Surgery in Patients With Localized (Non-Metastatic) Rectal Cancer, RAC#2011 031.

Investigators: Bazarbashi S, Abduljabbar A, Al-Sanea N, El-Foudeh M, Memon M and Khafaga Y

PROJECT DESCRIPTION
Protocol.

PROGRESS

Active.

Project Title: A Phase I-II Trial of Capecitabine (Xeloda), Oxaliplatin and Irinotecan in Combination With Bevacizumab in 1st Line Treatment of Metastatic Colorectal Cancer, RAC#2081-068.

Investigators: Bazarbashi S, Al-Jubran A, Hussein S, Darweesh A, Abdelsalam M, Ahmed M, Al Zahrani A and Colcol E

PROJECT DESCRIPTION

Protocol.

PROGRESS

Active.

Project Title: Phase II Prospective Study of the Clinical Efficacy of Autologous SCT in patients With Critical Limb Ischemia, RAC#2081-026.

Investigator: Al-Zahrani H

PROJECT DESCRIPTION

Protocol.

PROGRESS

Active.

Project Title: The Combination of GnRh Analogue and Aromatase Inhibitor in Receptor Positive Premenopausal Women With Advanced Breast Cancer A Prospective Trial, RAC#2081-064.

Investigators: Alsayed A, Twegieri T, Ajarim D, Ismail K, Pat R, Al-Zahrani A, Hussein S, Abdelsalam M, Abuzeid M, Colcol E and Shoukri M

PROJECT DESCRIPTION

Protocol.

PROGRESS

Active.

Project Title: RATG AA07: Prospective Phase II Study of Rabbit Antithymocyte Globulin (ATG, Thymoglobuline[®], Genzyme) With Cyclosporin for Patients With Acquired Aplastic Anaemia and Comparison With Matched Historical Patients Treated With Horse ATG and Cyclosporin: A Study from the European Blood and Marrow Transplant (EBMT) Severe Aplastic Anaemia Working Party, RAC#2081-005.

Investigators: Al-Zahrani H, Al-Mohareb F, Aljurf M, Al-Sharif F, Chaudhri N, Mohamed SY, Al-Anazi K, Saleh AJM and Bakr M

PROJECT DESCRIPTION

Protocol.

PROGRESS

Active.

Project Title: A Randomized Multicentre Study Comparing GCSF Mobilized Peripheral Blood and GCSF stimulated Bone Marrow in patients Undergoing Matched Sibling Transplantation for Hematologic Malignancies (20081-076).

Investigator: Aljurf M

PROJECT DESCRIPTION

Protocol.

PROGRESS

Active.

Project Title: An open-label, Multi-Center, Expanded Access Study of RAD001 in Patients With Metastatic Carcinoma of the Kidney Who Are Intolerant of or Have Progressed Despite Any Available Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy, RAC#2081-094.

Investigator: Bazarbashi S

PROJECT DESCRIPTION

Protocol.

PROGRESS

Pending approval.

Project Title: Use of 18F-Fluorodeoxyglucose (FDG) Position Emission Tomography (PET) as a predictor of residual disease and subsequent relapse in patients With Non Hodgkin's Lymphoma (NHL) and Hodgkin's Lymphoma (HL) undergoing High Dose Chemotherapy (HDC) and (ASCT), RAC#2041 050.

Investigators: Akhtar S, Al-Sugair A, Al-Kadhi Y, Bazarbashi S, Maghfoor I, Abdelsalam M, Khafaga Y, Nabil M and Al-Mohailaeb F

PROJECT DESCRIPTION

Protocol.

PROGRESS

F/U.

Project Title: The Prognostic Significance of BCL2 & BCL6 Expression in DLBCL Treated by CHOP or R-CHOP. Retrospective Study, Single Institute Experience, RAC#2071 061.

Investigators: Soudy H, Tbakhi A, Akhtar S, Maghfoor I, Eltayb M, Abdelsalam M and Elkhalfifa M

PROJECT DESCRIPTION

Protocol.

PROGRESS

Active.

Project Title: (ALIMTA Study) A Randomized Phase II Study Comparing Pemetrexed Plus Best Supportive Care With Best Supportive Care as Maintenance, Following First Line Treatment With Pemetrexed-Cisplatin in Patients With Advanced Non-Small Cell Lung Cancer (2071-073).

Investigator: Maghfoor I

PROJECT DESCRIPTION

Protocol.

PROGRESS

Active.

Project Title: GORG-001 A Multicenter Prospective Phase II Trial of Neo-Adjuvant (FEC 100)/Cisplatin - Docetaxel ± Trastuzumab in Women Who Over Expressed or Amplified Her2/neu With Locally Advanced Breast Cancer, RAC#2061-048.

Investigator: Twegieri T

PROJECT DESCRIPTION

Protocol.

PROGRESS

Active.

Project Title: SWOG 0777: A Randomized Phase III Trial of CC-5013 (Lenalidomide, NSC-703813) and Low Dose Dexamethasone (LLD) Versus Bortezomib (PS-341, NSC-681239), Lenalidomide and Low Dose Dexamethasone (BLLD) for Induction, in Patients With Previously Untreated Multiple Myeloma Without an Intent for Immediate Autologous Stem Cell Transplant, RAC # 2081 113.

Investigator: Chaudhri N

PROJECT DESCRIPTION

Protocol.

PROGRESS

Approved for accrual

Project Title: SWOG 0230 Phase III Trial of LHRH Analog Administration During Chemotherapy to Reduce Ovarian Failure Following Chemotherapy in Early Stage, Hormone-Receptor Negative Breast Cancer, RAC#2091-013.

Investigators: Alsayed A, Ajarim D, Twegieri T, Al-Shabanah M, Darwish A, Ahmed MN, Tulbah A and Retuta R

PROJECT DESCRIPTION
Protocol.

PROGRESS
In progress.

Project Title: GORG – 002 Randomized Phase III Trial to Determine the Effectiveness of Vitamin D3 (Cholecalciferol) Given With Docetaxel Versus Docetaxel in Patients With Metastatic Breast Cancer., RAC#2091-009.

Investigators: Twegieri T, Ajarim D, Al-sayed A, Al-Shabanah M, Tulbah A, Raef H, El-Shaker and Retuta R

PROJECT DESCRIPTION
Protocol.

PROGRESS
In progress.

Project Title: Phase II Study of Vincristine, Adriamycin, Actinomycin, Ifosfamide Combination Chemotherapy in Ewing's Sarcoma, RAC#2031 065.

Investigators: Memon M, Al-Dayel F, Ahmad J and Allam A

PROJECT DESCRIPTION
Protocol.

PROGRESS
Active.

Project Title: A Multi-National, Randomized, Phase III, GCIG Intergroup Study Comparing Pegylated Liposomal Doxorubicin (CAELYX®) and Carboplatin vs. Paclitaxel and Carboplatin in Patients With Epithelial Ovarian Cancer in Late Relapse (>6 months):GCIG CALYPSO STUDY, RAC#2051-062.

Investigator: Al-Jubran A

PROJECT DESCRIPTION
Protocol.

PROGRESS
F/U.

Project Title: Phase II Study of Neo-adjuvant Chemotherapy With Doxorubicin Followed by Docetaxel-Cisplatin in Locally Advanced Breast Cancer, RAC#2011022.

Investigators: Ezzat A, Rahal M, Bazarbashi S, Ajarim D, Inrahim E, Twegieri T, Akhtar SS, Maghfoor I, Al-Malik O, Al-Shabanah M, Tulbah A, Raja M, Pai C, El Foudeh M and El Weshi

PROJECT DESCRIPTION
Protocol.

PROGRESS
F/U.

Project Title: Phase II Trial of Concurrent Administration of Intravesical BCG and Interferon 2-B in the Treatment and Prevention of Recurrence of Superficial Transitional Carcinoma of the Urinary Bladder, RAC#2011-073.

Investigators: Bazarbashi S, Raja M, Rehman K, Rahal M, El-Foudeh M, El-Weshi A, Pai C and Shoukri M

PROJECT DESCRIPTION
Protocol.

PROGRESS
Active.

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: Alsayed A, Ajarim D, Twegieri T, Al-Shabanah M, Al-Malik O, Tulba A, Abdelsalam M, Al-Zahrani A and Fatani D

PROJECT DESCRIPTION
Protocol.

PROGRESS
Active.

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, Balaraj, Munkara A, Al-Shabanah M, Hussein F, Al-Dayel F and Gesell A

PROJECT DESCRIPTION
Protocol.

PROGRESS
Pending approval.

Project Title: RTOG 0227 Phase I/II Study Of Pre-Irradiation Chemotherapy With Methotrexate, Rituximab, and Temzolomide And Post-Irradiation Temzolomide For Primary Central Nervous System Lymphoma, RAC#2081-049)

Investigators: Al Rajhi N, Khafaga Y, Al-Shabanah M, Akhtar S, Maghfoor I and Gesell A

PROJECT DESCRIPTION
Protocol.

PROGRESS
Active.

Project Title: RTOG 0627 Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme, RAC#2081-013.

Investigators: Al Rajhi N, Memon M, Al-Hebshi A, Al-Shabanah M, Suhaibani H, Hussein F and Gesell A

PROJECT DESCRIPTION
Protocol.

PROGRESS
On Hold.

Project Title: RTOG 0614 A Randomized, Phase III, Double-Blind, Placebo-Controlled Trial Of Memantine For Prevention Of Cognitive Dysfunction In Patients Receiving Whole-Brain Radiotherapy, RAC#2081- 2081-054.

Investigators: Al Rajhi N, Al-Hebshi A, Memon M, Al-Shabanah M, Hussein F and Gesell A

PROJECT DESCRIPTION
Protocol.

PROGRESS
Pending.

Project Title: RTOG 0235 ACIN 6668 Positron Emission Tomography Pre- and Post-treatment Assessment for Locally Advanced Non-Small Cell Lung Carcinoma, RAC#2081-038.

Investigators: Al Rajhi N, Al-Sugair A, Al-Hebshi A, Maghfoor I, Abouzeid M, Hussain F and Gesell A

PROJECT DESCRIPTION
Protocol.

PROGRESS
Active.

Project Title: RTOG 0415 A Phase III Randomized study of Hypofractionated 3D-CRT/IMRT Versus Conventionally fractionated 3D-CRT/IMRT in patients With Favorable-Risk Prostate Cancer, RAC#2081-116.

Investigators: Al Rajhi N, Balaraj K, Al-Shabanah M and Fatani D

PROJECT DESCRIPTION
Protocol.

PROGRESS

Pending approval.

Project Title: RTOG 0524 A Phase I/II trial of a Combination of Paclitaxel and Trastuzumab With Daily Irradiation or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery for Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer, RAC#2081-116.

Investigators: Al Rajhi N, Bazarbashi S, Al-Jubran A, Balaraj K, Al-Shabanah M and Abdelmoety D

PROJECT DESCRIPTION

Protocol.

PROGRESS

Active.

Project Title: KFSH ALL 1423 Protocol, RAC#2021-050.

Investigators: Sahovic E, Aljurf M, Chaudhri N, Al-Sharif F, Al-Mohareb F, Al-Shanqeeti A, Al-Zahrani H and Morshed M

PROJECT DESCRIPTION

Protocol.

PROGRESS

Active.

REGISTRY

Project Title: Protocol Amendment No.1-Adjuvant Colon Cancer w/ ELOXatin®/5 FU Based Regimen: ACCELOX, RAC#2071 027.

Investigators: Al-Jubran A and Bazarbashi S

PROJECT DESCRIPTION

Registry.

PROGRESS

Active.

Project Title: A worldwide Observational Registry Collecting Longitudinal Data on the Management of CML Patients in Routine Practice, RAC#2081-025.

Investigators: Chaudhri N, Al-Mohareb M, Aljurf M, Sharif F, Al-Zahrani H, Yousuf S, Saleh AJM, Bakr M, Nassar A, Ahmed SO, Al-Tanbal H, Hussein F and Colcol E

PROJECT DESCRIPTION

Registry.

PROGRESS

Active.

Project Title: Validation of the Arabic Questionnaire for Symptom Assessment, RAC# 2061 049.

Investigators: Al-Shahri, Ali Al-Zahrani, Samy Alsirafy and Mohamed Shoukri

PROJECT DESCRIPTION

Prospective Study

PROGRESS

Active.

Project Title: The Utilization of Radiation Therapy Services by a Palliative Care Service, RAC# 2061054.

Investigators: Mohammad Al-Shahri, Medhat El-Sebaei and Amin Al-Omir

PROJECT DESCRIPTION

Prospective Study

PROGRESS

Active.

Project Title: Prospective Data Collection of Newly Diagnosed Hodgkin's Disease and Non-Hodgkin's Lymphoma Cases, RAC# 2021-048.

Investigators: Maghfoor I, Akhtar S, Abdelsalam M, Khafaga Y, Bakshi NA and Elkhalifa M

Project Title: Use of Antimicrobials in the Last Week of Life in Palliative Care Unit, KFSHRC, RAC # 2081069.

Investigators: Mohammad Al-Shahri, Mohammed Al-Shaqi, Ali Al-Zahrani, Ahmad Alami, Abdulrahman Bin-Muammar and Batlah Al-Murshed

PROJECT DESCRIPTION

Retrospective Study

PROGRESS

Active.

Project Title: Referral Pattern to a Palliative Care Program, RAC # 2081071.

Investigators: Mohammad Al-Shahri, Samy Alsirafy and Mahmoud Sroor

PROJECT DESCRIPTION

Retrospective study

PROGRESS

Active.

PUBLICATIONS

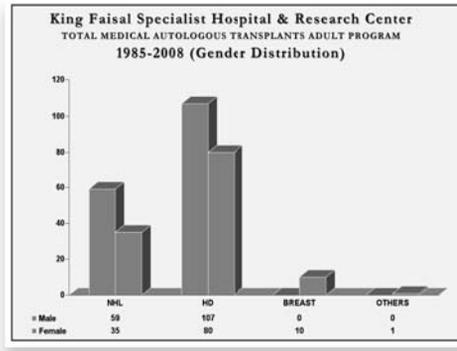
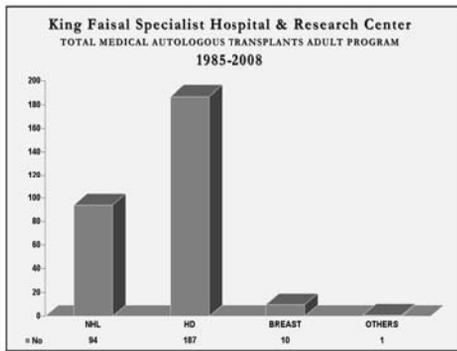
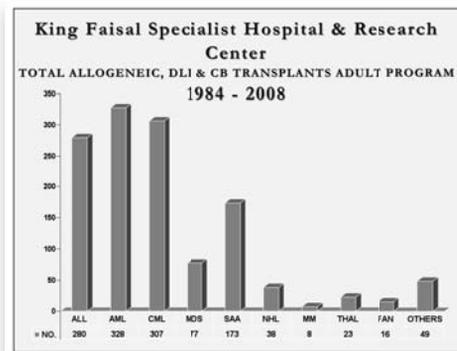
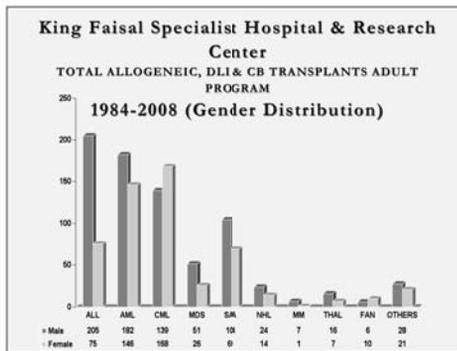
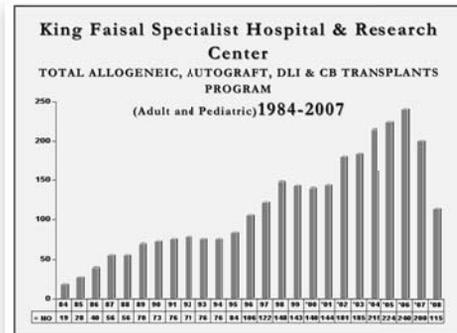
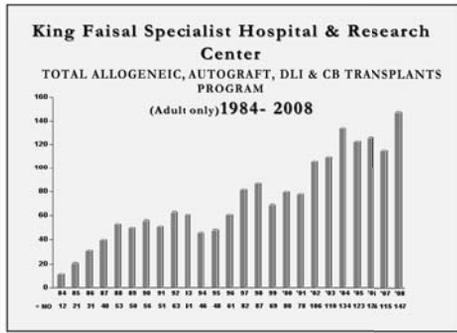
- Association between XRCC1 G399A polymorphism and late complications to radiotherapy in Saudi head and neck cancer patients. G. Alsbeih, M. El Sebaie, N. Al-Rajhi, N. Al-Harbi, G. Mohamed, K. Abu-Amero. *Journal of the Egyptian National Cancer Institute*, Cairo University, June 2008.
- Metastatic synovial sarcoma of the foot to the throat. Ali Aljubran, Asma Tulbah, Syed Akhtar. *American Journal of Clinical Oncology*, Volume 30, Number 1, February 2008.
- FOXP3 + Tregs and B7-H1 + PD-1 + T lymphocytes co-infiltrate the tumor tissues of high risk breast cancer patients: Implications of immunotherapy. Ghebeh H, Barhoush E, tulbah A. Elkum N, Twegjeri T. Dermime S. *BMC Cancer*, 2008 8:57, 23 February 2008.
- Factors affecting autologous peripheral blood stem cell collection in patients with relapsed or refractory diffuse large cell lymphoma and hodgkin's lymphoma: A single institution result of 168 patients. Saad Akhtar, Amr El Weshi, Mohammed Rahal, Yasser Khafaga, Abdelghani Tbakhi, Hind Humaidan, Irfan Maghfoor. *Leukemia and Lymphoma*, 2008; April; 49(4):769-78.
- Breast carcinoma associated fibroblasts and their counterparts display neoplastic specific changes. N. Hawsawi, H. Ghebeh, SF Hendrayani, A. Tulbah, M. Al Eid, T. Twegjeri, D. Ajarim, A. Alaiya, S. Darmime, A. Aboussekhra. *Cancer Research*, 68, 2717-2725, April 15, 2008.
- Gene expression profiling in women with breast cancer in Saudi population. Bin Amer SM, Maqbool Z, Nirmal MS, Qattan AT, Hussain SS, Jepre HA, Tulbah AM, Malik OA, Twegjeri T. *Saudi Med J*, 2008, April 29 (4):507-13.
- High dose chemotherapy and autologous stem cell transplantation for Hodgkin's lymphoma in the Kingdom of Saudi Arabia. Akhtar S, Abdelsalam M, El-Weshi A, Al Hussein H, Janabi I, Rahal M, Maghfoor I. *Bone Marrow Transplantation*, 2008;42, S37-S40.
- A modern regimen of pre-operative chemo-radiation therapy in locally advanced rectal cancer. Bazarbashi S, El, Bassiouni, Abdelsalam M, Soudy H, Al-Sanea N, Abdul Jabbar A, Manji M, Fagih M, Ajarim D. *J Surgical Oncology*, 2008 September 1:98(3):167-74.
- The impact of trisomy 12, retinoblastoma gene and P53 in prognosis of B-cell chronic lymphocytic leukemia. Abdelsalam M, El Sissy A, Samra Ma, Ibrahim S, El Markaby D, Gadallah F. *Hematology*, 2008 June 13(3):147-53.
- Phase II trial of neoadjuvant cisplatin, 5-fluorouracil and interferon-alpha in operable squamous cell carcinoma of the esophagus. S. Bazarbashi, M. Abdelsalam, T. Amin, M, El-Bassiouni, H. Soudy, A. El-Weshi, H. Al Husseni, K. Rehman, M. Memon, D. Ajarim. *Chemotherapy*, 54(4):315-22. Epub: 14 August 2008.
- Successful outcome of Langerhans cells histiocytosis complicated by therapy related myelodysplasia and acute myeloid leukemia. A case report. *Cases J*, 2008, August 18; 1(1):101.
- Acquisition of vernal and atopic keratoconjunctivitis after bone marrow transplantation. Tabbara KF, Nassar A, Ahmed SO, Al Mohareb F, Aljurf M. *Am J Ophthalmol*. 2008 Sep;146(3):462-5. Epub 2008 Jul 9.

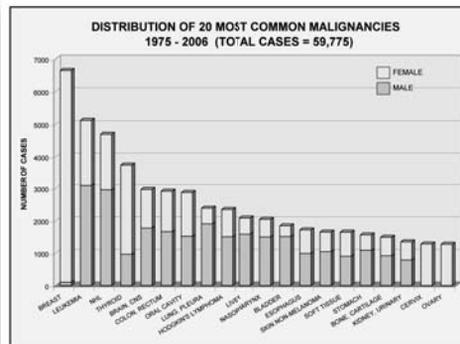
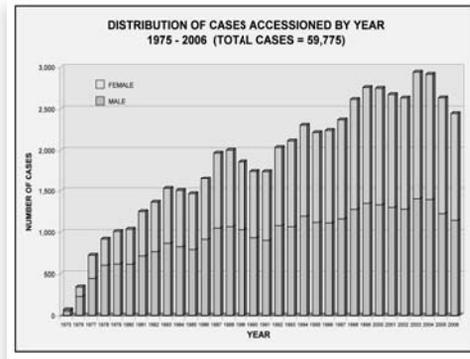
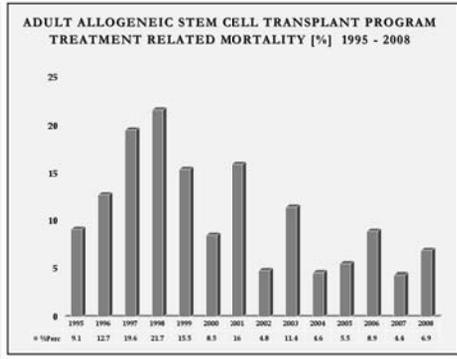
-
- ↪ The Wilms' tumor antigen is a novel target for human CD4+ regulatory T cells: implications for immunotherapy. Lehe C, Ghebeh H, Al-Sulaiman A, Al Qudaihi G, Al-Hussein K, Almohareb F, Chaudhri N, Alsharif F, Al-Zahrani H, Tbakhi A, Aljurf M, Dermime S. *Cancer Res.* 2008 Aug 1;68(15):6350-9.
 - ↪ The challenge of risk stratification in acute myeloid leukemia with normal karyotype. Syed Z. Zaidi, Tarek Owaidah, Fahad Al Sharif, Said Y. Ahmed, Naeem Chaudhri, Mahmoud Aljurf. *Hematol Oncol Stem Cell Ther* 2008; 1(3): 141-158.
 - ↪ An IMRT technique to increase therapeutic ratio of breast irradiation in patients with early stage left breast cancer: limiting second malignancies." Ahmed RS, John B Fiveash, Richard A Popple, Sharon A Spencer. Jennifer F. De Los Santos. *Medical Dosimetry*, 2008 Spring; 33 (1): 71-7.
 - ↪ Morphologic, immunophenotypic and clinical discriminators between T-cell /histiocyte rich large B cell lymphoma and lymphocyte predominant Hodgkin lymphoma. W. Mourad, S. Al Tahani, A Tabaki, M Al Omari, Y. Khafaga, M Shoukri, A El Weshi, M Al Shabanah, A Ezzat. *Hematol Oncol Stem Cell Ther* 1 (1), January 2008.
 - ↪ Factors affecting autologous peripheral blood stem collection in patients with relapsed or refractory diffuse large B cell lymphoma and Hodgkin's lymphoma: A single institution result of 168 patients. S Akhtar, A El Weshi, M Rahal, Y Khafaga, A Tbakhi, H Humaidan, I Maghfoor. *Leukemia and Lymphoma*, 2008.
 - ↪ Hodgkin lymphoma in very young children: Clinical characteristics and outcome of treatment. A Belgaumi, A Al Kofide, N Joseph, Y Khafaga, R Jamil-Malik, R Sabbah. *Leukemia and Lymphoma*, May 2008; 49(5):910-916.
 - ↪ Morphologic, immunophenotypic and clinical discriminators between T-Cell/Histiocyte Rich Large B Cell Lymphoma and Lymphocyte Predominant Hodgkin Lymphoma, W. Mourad, S. Al Thani, A. Tbakhi, M. Al Omari, Y. Khafaga, M. Shoukri, A. El Weshi. M. Al Shabanah and A. Ezzat. *Hematol Oncol Stem Cell Ther* 1(1), January 2008.
 - ↪ Expression of surviving and p16/Cdk6/pRB proteins and induction of apoptosis in response to radiation and cisplatin in meningioma cells. Al-Khalaf H, Lach B, Allam A, Hassounah M, Alkhani A, Elkum N, Alrokayan S, Aboussekhra A. *Brain Research*, 1188 (2008): 0025-34.
 - ↪ Alsirafy SA, Hassan AA, Al-Shhari MZ. Hospitalization pattern in a hospital-based palliative care program: An example from Saudi Arabia. *Am J Hosp Palliat Med*, 2009; 26(1): 52-6.
 - ↪ Alsirafy SA, Sroor MY, Al-Shahri MZ. Predictive impact of electrolyte abnormalities on the admission outcome and survival of palliative care cancer referrals. *J Palliat Med*, 2009; 12(2): 177-180.

ABSTRACTS AND PRESENTATIONS

- ↪ Outcome of chronic myeloid leukaemia patients with allogeneic haematopoietic stem cell transplantation and a low risk score in the imatinib era. A report from the EBMT Chronic Leukemia Working Party and European Leukemia Net D. Heim, R. Brand, E. Olavarria, J.F. Apperley, C. Crawley, A. Devergie, M. Aljurf, J. Holowiecki, T. Fuutu, L. Brinch, H.J. Kolb, T. de Witte, R. Hehlmann, A. Grathwohl. *Bone Marrow Transplantation* 41 Supplement, March 2008.
- ↪ Ocular findings following Allogeneic Hematopoietic Stem Cell Transplantation (HSCT). Khalid F. Tabbara, Ahmad Ghamdi, Fahad Almohareb, Amr Nassar, Mahmoud Aljurf. Joint Meeting of the American Academy of Ophthalmology and European Society of Ophthalmology (SOE), 2008.
- ↪ CD4+ regulatory T cells specific for the WT1 antigen are present in acute myeloid leukemia patients: Implication for immunotherapy. Said Dermime, Cynthia Lehe, Hazem Ghebeh, Abdullah Al Sulaiman, Ghofran Al Qudaihi, Khaled Al Hussein, Fahad Al Mohareb, Naeem Chaudhri, Fahad Alsharif, Hazzaa Al Zahrani, Said Y Mohamed, Abdelghani Tbakhi, Mahmoud Aljurf. *Blood Supplement* 2008.
- ↪ Enhancement of lytic activity of leukemia cells by CD8+ cytotoxic T lymphocytes generated against a WT1 peptide analogue. Ghofran Al Qudaihi, Cynthia Lehe, Muna Negash, Monther Al-Alwan, Haem Ghebeh, Said Yousuf Mohamed, Abu-Jafar Mohammed Saleh, Hind Al-Humaidan, Abdelghani Tbakhi, Anne Dickinson,

- Mahmoud Aljurf, Said Dermime. Accepted for publication, *Leukemia & Lymphoma Journal*, 22 Oct 2008.
- ↔ Autologous bone marrow transplantation for extramedullary plasmacytoma presenting as extensive bilateral Adrenal Tumors. Ahmed Mohammed, Abdullah AlGhamdi, Al-Omari Monahammed, Aljurf Mahmoud, Yusuf Al-Kadhi. Accepted for publication, *Annals of Saudi Medicine*, 2008.
 - ↔ High efficacy and low toxicity of APL induction with concurrent Idarubicin/ATRA followed by a novel and simplified outpatient post remission therapy using single doses of idarubicin and intermittent ATRA. M Aljurf, F Alqurashi, F Al Mohareb, E Sahovic, F Al Sharif, H Al Zahrani, A Al Shanqeeti, T owaidah, A Iqbal, S Z Zaidi, Z A Nurgat, M Sanz, N Chaudhri. Accepted for publication in the *Annals of Hematology*. 2008.
 - ↔ High efficacy and low toxicity of “short course oral Valganciclovir” given as one week BID treatment and one week QD maintenance as pre-emptive therapy for post HSCT CMV infection. AJ. Saleh, F. Al Mohareb, F. Al-Rabiah, N. Chaudhri, F. Alsharif, H. Al-Zahrani, S. Mohamed, M. Bakr, S. Ahmed, A. Nassar, F. Hussain, Z. Nurgat, H. Al-Abdely, M. Aljurf. *Blood* (abstract) submitted.
 - ↔ Ocular findings following Hematopoietic Stem Cell Transplantation. K. Tabarra, A. Ghamdi, F. Al Mohareb, N. Chaudhri, F. Alsharif, H. Al Zahrani, S. Mohamed, A. Nassar, M. Aljurf. American Academy of Ophthalmology Annual Meeting Nov 8-11, 2008.
 - ↔ CD4+ regulatory T Cells specific for the WT1 Antigen are present in acute myeloid leukemia patients: Implication for immunotherapy. S. Dermime, C. Lehe, H. Ghebeh, A. Al Sulaiman, G. Al Qudaihi, K. Al Hussein, F. Al Mohareb, N. Chaudhri, F. Alsharif, H. Al Zahrani, S. Mohamed, A. Tbakhi, M. Aljurf. *Blood* (ASH Annual Meeting Abstracts), Nov 2008; 112: 1933.
 - ↔ Outcome of chronic myeloid leukemia patients with allogeneic hematopoietic stem cell transplantation and a low risk score in the imatinib era. A report from the EBMT chronic Leukemia Working Party and European Leukemia Net. D. Heim, R. Brand, E. Olavarria. *Bone Marrow Transplantation* 41 Supplement, March 2008.
 - ↔ Ocular findings after allogeneic stem cell transplantation. S. Yousuf. Joint Meeting of the American Academy of Ophthalmology and European Society of Ophthalmology (SOE), November 8-11, 2008.
 - ↔ Ocular findings following allogeneic HSCT. K. Tabarra, A. Ghamdi, F. Al Mohareb, N. Chaudhri, F. Alsharif. Association of Research in Vision and Ophthalmology (ARVO) 27 April-01 May 2008.
 - ↔ Introduction to pain and palliative care in cancer patients. M. El-Foudeh. Abstract book, Updates in Gynecology & Women's Health Int'l. Conference, Riyadh, KSA October, 2008.





THE KING FAISAL
HEART INSTITUTE

The King Faisal Heart Institute

The King Faisal Heart Institute (KFHI) is committed to excellence in patient care, teaching, and research. Its mandate includes research on the challenges of cardiovascular diseases facing the people of Saudi Arabia and its objective is to increase scientific knowledge of cardiovascular diseases, including their epidemiology, risk and risk factors, prevention, detection and diagnosis, treatment and prognosis, and to initiate cardiovascular, evidence-based programs.

In 2008 the KFHI had 33 approved/ongoing research projects and 9 research projects which were completed. These projects included retrospective records review and analysis, registries, interventional, diagnostic, basic research, and animal studies. All sections of the KFHI have research proposals as follows: adult cardiology = 7, adult cardiovascular surgery = 7, pediatric cardiology = 8, pediatric cardiovascular surgery = 7, adult and pediatric cardiovascular surgery = 3, general = 1.

The KFHI continues to develop its Strategic Research Plan (SRP) which is designed to develop and sustain significant, internationally acknowledged research in several thematic areas relevant to the high incidence of cardiovascular diseases in the Kingdom. The KFHI plans to significantly increase its research capacity in each of these areas over the next five years and to become recognized internationally for its high caliber research.

Director:

Charles C. Canver, MD

RESEARCH PROJECTS

Project Title: Congenital Heart Disease Registry, RAC #: 991026.

Principal Investigator/s: Drs. Mansour Al Jufan and Zohair Al-Halees

PROJECT DESCRIPTION

This Registry is a collaborative project between the KFHI and the Biostatistics, Epidemiology and Scientific Computing Department, Research Centre to collect data on pediatric patients with congenital heart disease.

PROGRESS

This Registry is on-going.

Project Title: Pediatric Heart Catheterization Registry, RAC #: 2001053.

Principal Investigator: Dr. Fadel Al Fadley

PROJECT DESCRIPTION

The aim of this Project was to establish a Registry for all diagnostic and interventional pediatric cardiac catheterizations performed at the KFSH&RC.

PROGRESS

This is an ongoing Registry. The cumulative number of subjects enrolled during the lifetime of the Project is 2279.

The number of subjects enrolled during the last approval year is 572.

Project Title: Mitral Balloon Valvotomy Registry Database, RAC #: 2001054.

Principal Investigator: Dr. 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 is an ongoing Registry. The cumulative number

of subjects enrolled during the lifetime of the Project is 675 patients.

Project Title: Valve Registry, RAC #: 2001055.

Principal Investigator: Dr. Zohair Al Halees

PROJECT DESCRIPTION

This Registry includes data on KFSH&RC patients (both adult and pediatric) who underwent valve surgery. Data on these patients' pre-operative, peri-operative, post-operative and follow-up course, including data on events such as thromboembolism, endocarditis, rhythm variations, anticoagulation, anticoagulation-related bleeding, readmissions, re-operations, symptomology and medications has been collected.

PROGRESS

This is an ongoing Registry. The cumulative number of subjects enrolled during lifetime of the Project is 6961.

The number of subjects enrolled during the last approval year is 507.

Project Title: Percutaneous Transluminal Coronary Angioplasty (PTCA) Registry, RAC #: 2001057.

Principal Investigator: Dr. Hani Al Sergani

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

This is an ongoing Registry. The cumulative number of subjects enrolled during the lifetime of the Project is 2671.

The number of subjects enrolled during last approval year is 267.

Project Title: KFHI Surgery Registry, RAC #: 2001058**Principal Investigator:** Dr. Zohair Al Halees**PROJECT DESCRIPTION**

This Registry includes all cardiovascular surgical procedures performed at the KFSH&RC and is utilized as a valuable research and program administrative tool.

PROGRESS

This is an on-going Registry. The cumulative number of subjects enrolled during the lifetime of the Project is 25617

The number of subjects enrolled during last approval year is 2588.

Project Title: Optimal Approach of Atrioventricular Insufficiency in Fontan Patients, RAC #: 2021017.**Principal Investigator:** Dr. Ahmad Sallehuddin**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. The Final Report was accepted by the RAC and recommended the closure of the project on 25 May 2008.

Project Title: Outcomes of Contegra Grafts, RAC #: 2021049.**Principal Investigator:** Dr. Ahmad Sallehuddin**PROJECT DESCRIPTION**

This retrospective review examined the outcomes of patients who received the Contegra biological valve conduit as an alternative to homografts.

PROGRESS

The study was completed and the Final Report was accepted by the RAC in August 2008. Sixty-three

patients were enrolled in the Study. The result showed that the addition of rings on the Contegra valve conduit resulted in a lower freedom from graft failure. No positive impact was seen in reducing conduit dysfunction.

Project Title: Fate of Bicuspid Neo-Aortic Valve in Arterial Switch Operation, RAC #: 2021058.**Principal Investigator:** Dr. Shahid Khan**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 study was completed and the Final Report was accepted by the RAC in 22 March 2008. The results clearly showed that, in our experience, tricuspid valve in transposition of great arteries (TGA) is not a contraindication to proceed with ASO.

Project Title: Retrospective Medical Records Review of Truncus Arteriosus, RAC #: 2031015.**Principal Investigator:** Dr. Ahmed AlOmrani**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 reviewed and collected on 60 patients.

Project Title: Tetralogy of Fallot (TOF): A Retrospective Chart Review, RAC #: 2031061.**Principal Investigator/s:** Dr. Saud Al Oufi

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.

Project Title: Is Myomectomy Justifiable in Preventing Recurrence of Discrete Subaortic Obstruction? RAC #: 2031072.

Principal Investigator: Dr. Zohair Al Halees

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.

Project Title: Effect of Percutaneous Coronary Intervention (PCI) on Diabetic Patients, RAC #: 2031082.

Principal Investigator: Dr. Walid Hassan

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

The data has been cleaned and validated on

approximately 450 of the 680 records identified as meeting the study criteria.

Project Title: The Impact of the Right Ventricular To Pulmonary Artery Shunt on the Early Outcome of the Modified Norwood Procedure, RAC #: 2041041.

Investigator: Dr. Zohair Al Halees

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

One hundred and thirty-one patients who meet the study criteria had been identified and reviewed. The data has been collected, validated and analyzed.

Project Title: Does Modified Ultrafiltration Affect the Clinical Outcome Following Congenital Heart Surgery? RAC #: 2041065

Principal Investigator/s: Dr. Mamdouh Al Ahmadi

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.

Project Title: Long-Term Outcome of Mitral Valve Repair Versus Mitral Valve Replacement Using Mechanical and Bioprosthetic Valves, RAC #: 2051016.

Principal Investigator: Dr. Zohair Al Halees

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

The data has been cleaned and validated on approximately 761 of 779 records identified as meeting the Study criteria.

Project Title: Permanent Pacing in Pediatric Patients: the King Faisal Specialist Hospital Experience, RAC #: 2051040.

Principal Investigator: Dr. Majid Al Fayyadh

PROJECT DESCRIPTION

This is a retrospective review to evaluate the experience and long term results of pacemaker (PM) therapy in children treated at the KFHS&RC.

PROGRESS

This project originally collected data on patients seen at the KFHI from 1985 – 2003. The Project has been expanded to include patients seen at the KFHI up to the end of 2008.

Project Title: Long-term Outcome of Aortic Valve Replacement Using the Ross Procedure in KFHI, RAC #: 2051055.

Principal Investigator: Dr. Zohair Al Halees

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

This study was completed and Final Report was accepted by RAC in December 2008. Study conclusion was that the Ross procedure is an attractive option for aortic valve replacement particularly in the young. It offers many advantages: silent, non-thrombogenic, requiring no anticoagulation, normal hemodynamics even at maximum exercise, has potential for growth, infection resistant. Between Jan 1990 – Dec 2006, 476 patients underwent Ross procedure for various aortic valve pathologies: 65% rheumatic and 35% nonrheumatic, mostly congenital. These two groups behaved differently regarding late autograft failure: congenital / non rheumatic AV disease with excellent outcomes and rheumatic AV disease with less favorable outcomes. We concluded that the Ross procedure with appropriate patient selection is effective and improves patient outcomes.

Project Title: Chlamydia Pneumoniae Deoxyribonucleic Acid (C. Pneumoniae DNA) & Coronary Artery Disease: A Pilot Study, RAC #: 2051061.

Principal Investigator: Dr. Walid Hassan

PROJECT DESCRIPTION

This prospective, randomized pilot-study primarily focused 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 CRP, BNP, Angiotensin II and Troponin T.
- d. the underlying inflammatory process associated with atherosclerosis and *C. Pneumoniae*.

PROGRESS

This study was completed and Final Report was accepted by RAC in December 2008. Our results showed that *C. Pneumoniae*' is not assigned as a coronary risk factor for our geographical region

Project Title: Clopidogrel and Hemorrhage in Coronary Artery Bypass Grafting (CABG): A Retrospective Study, RAC #: 2061004.

Principal Investigator: Dr. Shahid Khan

PROJECT DESCRIPTION

This retrospective Study is evaluating 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

Data collection from the medical records is almost completed. Transfusion data will be collected from the Blood Bank to help validate data before analysis.

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.

Principal Investigators: Drs. Fareed Khouqeer and Ziad Issa

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

The medical records have been reviewed on approximately 35 of the 61 patients who met the study criteria; data collection is ongoing.

Project Title: Early and Long-term Outcomes and Follow-up of Mechanical Valve Replacement in Patients Less than 15 Years of Age, RAC #: 2061029

Principal Investigator/s: Dr. Elias Saad

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

The medical record of 228 patients have been reviewed; preliminary data has been collected. Echocardiograph reports are currently being assessed.

Project Title: Prospective Trial of Endoscopic versus Conventional Vein Harvesting Techniques for CABG: Morphology and Post-Operative Outcome, RAC #: 2061034.

Principal Investigator/s: Drs. Charles Canver and Sajjad Yousafzai

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 is ongoing.

Project Title: The Impact of Palliative Procedures on the Growth of Pulmonary Arteries in Pulmonary Atresia With Ventricular Septal Defect, RAC #: 2061041.

Principal Investigators: Drs. Akram Allam and Ahmad Sallehuddin

PROJECT DESCRIPTION

This retrospective Study is evaluating 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.

PROGRESS

The medical records have been reviewed on approximately 25 of the 49 patients identified as meeting the study criteria; a second review of all catheterization films and surgery data is currently in Progress.

Project Title: NT-Pro-Brain Natriuretic Peptide (BNP) Levels in Neonates With and Without Cardiac Disease – a New Method to Detect Cardiac Causes of Respiratory Insufficiency in Neonates, RAC #: 2061068.

Principal Investigator: Dr. Ghassan Siblini

PROJECT DESCRIPTION

This prospective randomized, stratified study will assess blood NT-Pro-BNP 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. The aims of the Study are to confirm the normative levels of NT-Pro-BNP and Troponin-T in a sample of healthy Saudi neonates and premature infants and to compare these values to NT-Pro-BNP levels in premature infants with congenital heart disease.

PROGRESS

Twenty patients, 5 cases and 16 controls, have been enrolled. Enrollment and data collection are ongoing.

Project Title: PANORAMA: An Observational Study, RAC #: 2061075.

Principal Investigator/s: Dr. Majid Al Fayyadh

PROJECT DESCRIPTION

This Study is collecting epidemiological data on patients who have Medtronic implantable pulse generators and implantable cardioverters/ defibrillators.

The aims of this post-marketing study are to:

- investigate the long-term operation of the devices and device features;
- assess the frequency and duration of heart-failure related hospitalizations;
- analyze temporal aspects of cardiovascular events and symptoms;
- describe the incidence and prevalence of ventricular and atrial arrhythmias;
- associate cardiovascular events and symptoms with device data and diagnostics;
- determine programming preferences considering physical assessment variables and pathologies;
- build a prognostic model of time to death by using population baseline variables as predictors.

PROGRESS

Fifty-seven patients have been enrolled. Enrollment and data collection are ongoing.

Project Title: Pulmonary Atresia With Intact Ventricular Septum: Initial Management and Follow-up (Retrospective Review), RAC #: 2071005.

Principal Investigator: Dr. Mansour Al Joufan

PROJECT DESCRIPTION

Pulmonary atresia 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.

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.

Project Title: Surgical Preparation for a Non-Surgical Fontan (NSF), RAC #: 2071006.

Principal Investigator: Dr. Bahaaldin Al Soufi

PROJECT DESCRIPTION

The objective of the study is to determine the overall outcome of NSF that is extended to non-high-risk patients requiring Fontan completion.

PROGRESS

This study is open to enrollment.

Project Title: Can Echocardiography Replace Cardiac Catheterization in the Pre-Operative Evaluation of Tetralogy of Fallot? RAC #: 2071015.

Principal Investigator: Dr. Zohair Al Halees

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. We will compare its accuracy with angiography and findings at surgery.

PROGRESS

This Study is ongoing.

Project Title: Transcatheter Closure of Patent Ductus Arteriosus in Patients \leq 8 kg, RAC #: 2071021.

Principal Investigator: Dr. Mansour Al Joufan

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.

PROGRESS

Data collection and analysis were completed on 26 patients. Preliminary data showed all patients were alive with no residual leak found at 6-month follow-up.

Project Title: Diagnostic Outcome Trial in Heart Failure (DOT-HF), RAC #: 2071039.

Principal Investigator: Dr. Majid Al Fayyadh

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

Six patients are enrolled and randomized in this Study. Follow-up is ongoing.

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.

Principal Investigator: Dr. Fareed Khouqeer

PROJECT DESCRIPTION

The aims of this Study were to:

- a. determine the mortality rates following congenital surgery at the KFHI
- b. rate the above patients according to the RACHS-1 scoring system
- c. compare the scores from the RACHS-1 scoring system with mortality rates at the KFHI

PROGRESS

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. We concluded that the RACHS-1 scoring system has excellent power to reasonably predict mortality in a non-North American, nor-European heart institute and it can discriminate between different categories of congenital heart surgery based on that predicted risk. This study was completed and Final Report was accepted by the RAC in March 2008.

Project Title: Outcomes and Risk Factors of Patients Undergoing ALCAPA at the KFSH&RC, RAC #: 2071067.

Principal Investigator: Dr. Bahaaldin Al Soufi

PROJECT DESCRIPTION

The Aims of this Study were to:

- a. report early (peri-operative) and time-related (follow-up range 1 month to 15 years) outcomes following surgery and examine risk factors for morbidity and mortality
- b. assess the pattern of recovery of left ventricular function and ischemic mitral regurgitation following successful surgery
- c. assess the accuracy of our theory that in patients in whom the anomalous coronary originates from a distant site on the pulmonary artery, and in whom direct transfer is not feasible, our modified implantation technique (see figure) allowing us

to avoid the risks of stretching and distortion is associated with equally good result despite the more complex surgical technique, and thus it is recommended in order to achieve the desired two coronary system repair

PROGRESS

This study was completed and the Final Report was accepted by RAC in July 2008. The study results showed excellent early and late outcomes with ALCAPA surgery utilizing a modified technique using aotologous flap extension of the abnormal artery from the aorta and pulmonary artery. Clinical echocardiographic follow-up was satisfactory. This technique can be recommended to all patients with ALCAPA.

Project Title: Transpericardial Access Training, RAC #: 2082002.

Principal Investigator: Dr. Fareed Khouqeer

PROJECT DESCRIPTION

The primary objective of this Study was to develop physicians' skills in perfecting transpericardial surgery (i.e. access to the heart and great vessels, then practicing suturing these anatomical structures) using a rodent model.

PROGRESS

Early in the Study it was obvious that the rodent model does not have any parietal pericardium and both pleurae were widely communicated. The Study was therefore terminated by the investigators and a Final Report was accepted by RAC in July 2008.

Project Title: A Non-Randomized, Retrospective Study to Compare the Clinical & Cost Effectiveness of Surgical Debridement & Delayed Primary Closure With Conservative Management of Post-Cardiac Surgical Wounds, RAC #: 2081014.

Principal Investigator/s: Dr. Sajjad Yousafzai

PROJECT DESCRIPTION

The aim of this study was to compare aggressive surgical debridement & delayed primary closure with the conservative management of wounds healing by secondary intention in order to evaluate the clinical effectiveness & cost effectiveness of the two methods.

PROGRESS

The surgical and wound data has been collected on 48 patients who met the Study criteria. Risk factor data collection is being collected before final analysis.

Project Title: A Retrospective Review of Intra-operative *In-Situ* Radial Artery Conduit Flow Assessment, RAC #: 2081027.

Principal Investigator: Dr. Charles C. Canver

PROJECT DESCRIPTION

The objectives of this Study were to:

- a. a) describe the KFHI experience in using this simple intra-operative technique that allows assessment of RA quality prior to its harvesting during CABG
- b. use the results of this study to validate this minimally-invasive, intra-operative technique for the assessment for RA quality prior to its complete harvesting during CABG.

PROGRESS

The results of the Study showed that this technique is acceptable for the intraoperative evaluation of the radial artery, in a busy tertiary center such as the KFSH&RC where otherwise patients would be placed on longer waiting lists to be evaluated by other sophisticated modalities. This study would make a platform for further larger prospective study. This study was completed and the Final Report was accepted by RAC in July 2008

Project Title: RE-LY AF Registry: Risk Factors, Treatments and Outcomes for Emergency Department Patients With Atrial Fibrillation in Multiple Regions of the World, RAC #: 2081033.

Principal Investigator: Dr. Yaseen Mallawi

PROJECT DESCRIPTION

Due to variations in medical practice and access to care, there is geographical variation in presentation and management of patients with atrial fibrillation. The aims of the study are:

- a. to determine variations in the predisposing conditions for atrial fibrillation and atrial flutter (AF/flutter) between different regions of the world and practice settings
- b. document regional variations in the management of AF/flutter and associated cardiovascular disease, including the frequency of anti-thrombotic and anti-hypertensive therapy and the degree of INR control and
- c. to document differences in the adverse cardiovascular outcomes of AF/flutter.

PROGRESS

Twelve subjects have been enrolled at the KFHI in this multi-center, international study. Enrollment, follow-up and data collection are ongoing.

Project Title: EnRhythm® MRI SureScan™ Pacing System, RAC #: 2081039.

Principal Investigator: Dr. Bandar Al Ghamdi

PROJECT DESCRIPTION

This project is a prospective, randomized controlled, unblinded, multi-center investigational study. The purpose is to confirm safety and efficacy in the clinical magnetic resonance imaging (MRI) environment of the investigational EnRhythm MRI SureScan Pacing System: implantable pulse generator (IPG) Model EMDR01, programmer software application Model SW005 and CapSureFix MRI active lead Model 5086MRI.

PROGRESS

One subject has been enrolled at the KFHI in this multi-center, international study. Follow-up and data collection are ongoing.

Project Title: Results of Open Heart Surgery in Patients With Sickle-Cell Trait or Disease at the KFSH&RC, RAC #: 2081055.

Principal Investigator: Dr. Sajjad Yousafzai

PROJECT DESCRIPTION

Reduced life expectancy coupled with tendency for complications in patients with sickle cell trait (SCT) or disease (SCD) is believed to negatively affect survival after open heart surgery. The aim of this study is to evaluate the outcome of open heart surgery in patients with sickle cell disease at KFSH&RC with particular emphasis on perioperative complications, early (30 days) & late mortality.

PROGRESS

Forty subjects Data collection is ongoing.

Project Title: Tricuspid Valve Replacement (TVR): Early (30 Days) Postoperative, One Year and Three Years Outcome, RAC #: 2081096.

Principal Investigator: Dr. Ahmad Moussa

PROJECT DESCRIPTION

The aims of the study are:

- a. to assess the early postoperative (30 days), 1 year and 5 years outcome in terms of survival, & the predictors of mortality, if any
- b. to study valve related complications and re-operation
- c. to study the benefits & disadvantages of mechanical & bio prosthesis in tricuspid valve replacement

Through this research it may be possible to identify key variables that affect patient outcomes in our patient population who undergo TVR. By identifying these variables the KFHI will be better able to screen high risk patients.

PROGRESS

Data collection is ongoing.

Project Title: Research to Design a Model for Community Consultation and Consent in Cardiovascular Research, RAC #: 2081097.

Principal Investigator: Marilyn Lockyer, RN, B.Sc., CCRP

PROJECT DESCRIPTION

The aims of this Study are to:

- a. investigate relevant legislation, guidelines, and principles guiding the concept of "community involvement" in biomedical research in Europe, the USA, Canada, Australia, South Africa and India
- b. ascertain the extent of community involvement in these countries, the models used to include community representation and how these models were developed
- c. explore lessons learned by researchers and government agencies in attempting to include community representation
- d. develop a compilation of current practices in community involvement.

PROGRESS

Data collection is ongoing.

Project Title: A Non-Randomized, Retrospective, Comparative Study to Examine the Incidence, Risk Factors, and Associated Mortality Rate of Acute Renal Failure (ARF) in Adult Patients Post Cardiac Surgery, RAC #: 2081102.

Principal Investigator/s: Dr. Ahmed Abdelrazik Osman

PROJECT DESCRIPTION

Acute renal failure requiring continuous renal replacement therapy post cardiac surgery carries a high mortality. Most studies have focused on patients with impaired renal function preoperatively but little is known about predictors of such complication in patients with preoperative normal renal function.

The aims of this study are:

- a. to determine the incidence, main risk factors, and hospital mortality rate for patients who develop

acute renal failure post cardiac surgery but who had normal renal function preoperatively

- b. to compare patients who developed renal failure with a historical group who did not develop renal failure to help identify how dealing with such a complication could be planned in advance, leading to potentially better outcomes and decreased its associated mortality and costs

PROGRESS

Data collection is ongoing.

PUBLICATIONS AND INTERNATIONAL PRESENTATIONS

ORIGINAL ARTICLE

- ↔ ME Fawzy, A Fathala, A Osman, MA Mostafa, G Mohamed, B Dunn. 22 Years Follow-up Result of Balloon Angioplasty for Discreet Native Coarctation of the Aorta in Adolescents and Adult. *American Heart Journal*. 2008; 156(5):910-915.
- ↔ ME Fawzy, M Stefadouros, S Elamroui, A Osman, E Ibrahim, O Nowayhed, A ElDali, C Canver. Long-Term (up to 18 Years) Clinical and Echocardiographic Results of Mitral Balloon Valvuloplasty in Children in Comparison with Adult Population. *Journal of Interventional Cardiology*. 2008 Jun; 21(3):252-9.
- ↔ ME Fawzy, M Shoukri, A Osamn, S Elamraoui, S Shah, O Nowayhed, C Canver. Impact of Atrial Fibrillation on the Immediate and Long Term Results of Mitral Balloon Valvuloplasty in 531 Consecutive Patients. *Journal of Heart Valve Disease*. 2008 Mar; 17(2):141-8.
- ↔ ME Fawzy, A Osman, V Nambiar, O Nowayhed, A ElDali, A Bader, C Canver. Immediate and Long-Term Results of Mitral Balloon Valvuloplasty in Patients with Severe Pulmonary Hypertension. *Journal of Heart Valve Disease*. 2008 Sep; 17(5):485-91.
- ↔ B Soufi, Z Bubul, M Joufan, F Khouqeer, C Canver, J Khalloghlian, A Sallehuddin, Z Halees. Surgical Strategy to Establish Dual-Coronary System for the Management of Anomalous Left Coronary Artery Origin from the Pulmonary Artery: Excellent Cardiac Recovery and Time-Related Survival. *Annals of Thoracic Surgery*. 2008 Jul; 86(1):170-6.

ABSTRACT / ORAL PRESENTATION

- ↔ ME Fawzy. Mitral Balloon Valvoplasty 18 Years Follow-Up: Effect of MBV on Left ventricular Function, Severe Pulmonary Hypertension and Severe Tricuspid Regurgitation. World Congress on Heart Disease. Toronto, Canada. July 2008.
- ↔ ME Fawzy, State of the Art Lecture - Percutaneous Mitral Balloon Valvotomy 18 Years Follow-up Results in 531 Consecutive Patients. Egyptian Society of Cardiology, Cairo, Egypt. February 2008.
- ↔ ME Fawzy, H Sergani, B Fadel, M Shahid, A Ghamdi, M Khandeel, S Shah. Immediate and Long-Term (up to 18 years) Results of Mitral Balloon Valvuloplasty in Patients with Extreme Pulmonary Hypertension. American College of Cardiology, Chicago, USA. March 2008.
- ↔ M Joufan, C Canver, W Hassan, A Omrani, S Oufi, Z Halees, M Khayat. Outcome and Complications of Percutaneous Peri-membranous VSD Closure in a Single Institution. American College of Cardiology, Chicago, USA. March 2008.
- ↔ F Khouqeer, A Sallehuddin, B Soufi, M Ahmadi, The Applicability of the Adjustment for Congenital Heart Scoring System for Stratification of Probability of Mortality Following Congenital Heart Surgery in an International Heart Institute. World Society of Cardio-Thoracic Surgeons, Kos Island Greece. May. 2008.
- ↔ E Saad, A Mousa, J Kalloghlian, B Afrane, Guy, C Canver. Tight Blood Glucose Control (TBGC) Decreases Surgical Wound Infection in Cardiac Surgical Patient Population in Intensive Care Unit. Saudi Heart Association, Riyadh, KSA. Feb. 2008.
- ↔ A Sehly, J Robinson, B Lee, G Taylor, D Ross, M Robertson, I Rebeyka. Pediatric Posternotomy Mediastinitis. Saudi Heart Association, Riyadh, KSA. Feb 2008.
- ↔ B Soufi, C ManIhiot, Mccrindle, M Ahmadi, A Sallehuddin, C Canver, Z Bubul, M Joufan, G Sibliini, Z Halees, B Fadel. Mechanical Valves Versus Ross Procedure for Aortic

-
- Valve Replacement in Children: Propensity-Adjusted Comparison of Long Term Outcomes. American Association for Thoracic Surgery. Boston, USA. May 2008.
- ↔ S Yousafazi, C Canver. Intraoperative In-Situ Radial Artery Conduit Flow Assessment. Innovations, Denver, USA. March. 2008.
 - ↔ B Fadel, B Soufi, Dekhyl, Z Bubul, A Sallehuddin, Z Halees. The Ross-Konno Procedure: Intermediate Term Clinical and Echocardiographic Follow-Up. American College of Cardiology, Chicago, USA. March 2008.
 - ↔ W Hassan, S Thawadi, J Bhuiyan, N Elkum, M Lockyer, Z Halees, C Canver. Chlamydia Pneumoniae Deoxyribonucleic Acid and Coronary Artery Disease: A Pilot-Study to Detect Chlamydia Pneumoniae Deoxyribonucleic Acid and Inflammatory Markers in Coronary Sinus during Coronary Angiography and Angioplasty. American College of Chest Physicians (ACCP), Philadelphia, Pennsylvania. 2008.

THE DEPARTMENT OF
LIVER TRANSPLANT & HEPATOBILIARY &
PANCREATIC SURGERY

The Liver Transplant & Hepatobiliary & Pancreatic Surgery

The 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 departments. Articles were published in the year 2008 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.

Chairman:

Mohammed Al Sebayel, MD

RESEARCH ACTIVITIES

Project Title: Pan Arab Liver Transplantation Registry, RAC No:2071 022.

Investigators: Hatem Khalaf, MD and Mohammed Al Sebayel, MD

PROJECT DESCRIPTIONS

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 & MAJOR FINDINGS

Since the approval of the registry by RAC in April 2007, the following tasks have been accomplished during 2008:

Phase I (Liver Transplant Patients at KFSH&RC): The department regularly updates the liver transplant patients' data up to this time.

Phase II (Liver Transplant patients in Saudi Arabia): Working on collaborating with Riyadh Military Hospital to incorporate their liver transplant patients data to the registry.

Phase II (Liver Transplant patients in Arab World): Added the Cairo University liver transplant patients data in the registry.

THE DEPARTMENT OF
PHYSICAL THERAPY

The Department of Physical Therapy

RESEARCH PROJECT

Chairman:

Project Title: The Effect of Static Stretching on the Dynamic Balance of the Saudi Recreational Football Players.

INTRODUCTION

Many researchers in the field of sports sciences have investigated the effects of stretching on sports performances. Recently, there have been rather controversial reports that some sport performances are negatively affected after stretching. It has been reported that muscle force development capability (Behm, Button, and Butt, 2001; Fowles, Sale and MacDougall, 2000), and power outputs around joints are reduced after stretching (Cornwell, Nelson, and Sidaway, 2002; Young and Elliott, 2001). The need to assess standing balance is important and has been recognized for many years (Gerbino, Griffin & Zurakowski, 2007). To date we are not aware of any study done on the effect of static stretching on static and dynamic balance for recreational football players in particular amongst Saudi Nationals.

PURPOSE OF THIS STUDY

Was to determine the effect of static stretching on static and dynamic balance of Saudi recreational football players.

HYPOTHESIS OF THIS STUDY

Static stretching will have a negative influence on the static and dynamic balance of Saudi recreational football players.

METHOD

Subjects: Forty healthy male Saudi recreational football players volunteered to participate in the study, mean age (20 -21) years, practicing football at least (3-4) times/week. Only right dominant leg subjects were included. **Study Design:** 2x3 repeated measures design; Subjects were randomly divided into two groups A (n=20) & B (n=20). Static and dynamic balances represented the primary outcome measures. Both groups performed static stretching exercises three times for each muscle group (Quadriceps, Hamstring, and Calf muscles). **Test procedure:** Balance Master System (Akbari et al, 2006) was used to measure static balance (SBT), while the Modified Star Excursion Balance Tests (Bressel et al, 2007) was used to measure the dynamic balance. Group A started SBT 1st and group B started DBT 1st.

DATA ANALYSIS

Data collected and analyzed using "SPSS (V.15)".

Results: The results demonstrated that static stretching has an immediate positive effect. However, the SBT results of group A increased post stretching. But the results indicated a significant main effect for groups ($P= 0.017$) and for the interaction between group and time ($P= 0.001$), but the main effect for time was not significant ($P= 0.533$). The DBT of both groups and for all 4 directions the main effect for time was significant,

while the main effect for group and the interaction between time and group was not significant. **Conclusion:** Static stretching has an acute positive effect on the static and dynamic balance of the Saudi recreational football players. Thus static stretching is useful for athletes who wish to increase their balance and flexibility during warm-up procedures, prior to exercise.

REFERENCES

- ↪ Akbari, M., Karimi, H., Farahini, H., & Faghhihzadeh, S. (2006). Balance Problems After Unilateral Ankle Sprains. *Journal Of Rehabilitation Research & Development*, 43,(7), 819-823.
- ↪ Behm, D. G., Button, D. C., & Butt, J. C. (2001). Factors affecting force loss with prolonged stretching. *Canadian Journal of Applied Physiology*, 26, 261-272.
- ↪ Bressel, E., Yonker, J.C., Kras, J., & Heath, E. M. (2007). Comparison of static and dynamic balance in female collegiate soccer, basketball, and gymnastics athletes. *Journal of Athletic Training*, 42,(1), 42-46.
- ↪ Cornwell, A., Nelson, A. G., & Sidaway, B. (2002). Acute effects of stretching on the neuromechanical properties of the triceps surae muscle complex. *European Journal of Applied Physiology*, 86, 428-434.
- ↪ Fowles, J. R., Sale, D. G., & MacDougall, J. D. (2000). Reduced strength after passive stretch of the human plantar flexors. *Journal of Applied Physiology*, 89, 1179-1188.
- ↪ Gerbino, P.G., Griffin, E.D., & Zurakowski, D.Z. (2007). Comparison of standing balance between female collegiate dancers and soccer players. *Gait & Posture*, 26, 501-507.
- ↪ Young, W., & Elliott, S. (2001). Acute effects of static stretching, proprioceptive neuromuscular facilitation stretching and maximum voluntary contractions on explosive force production and jumping performance. *Research Quarterly for Exercise and Sport*, 72, 273-279.

THE DEPARTMENT OF
SURGERY

The Department of Surgery

The Department of Surgery is dedicated to the best patient care, teaching and research. At the end of 2008, the department had 7 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:

Saif Al Sobhi, MBBS, ABIS, FRCS (Glas)

All divisions of Surgery have research proposals as follows:

- ∞ Breast
- ∞ Colorectal
- ∞ Endocrine
- ∞ General Minimally Invasive Surgery
- ∞ Ophthalmology
- ∞ Pediatric
- ∞ Plastic
- ∞ Renal Transplant
- ∞ Thoracic
- ∞ Vascular

The objective of the department is to increase scientific knowledge of different surgical cases 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.

RESEARCH PROJECTS

Project Title: Impact of Sleeve Gastrectomy on Iron Indices and Incidence of iron Deficiency and Anemia, RAC Proposal #: 2071-047.

Principal Investigator: Hakeam, Dr. Bamehriz

Co-Principal Investigator: Dr. Patrick O'Regan, Dr. Abdurahman Salem

PROJECT DESCRIPTION

Sleeve gastrectomy is a new restrictive bariatric procedure, where 70%-80% of the greater curvature of the stomach is resected. Generally, restrictive procedures have been associated with lower incidence of nutritional complications when compared with malabsorptive procedures. However, recent studies showed that iron deficiency is frequently observed after restrictive procedures. The incidences of anemia and iron deficiency after vertical banded gastroplasty are about 46% and 32%, respectively, as reported in a prospective study. The clinical consequences of iron deficiency are both hematologic and non-hematologic. Evidences have shown that iron deficiency without anemia affects cognition in adolescent girls and causes fatigue in adult women, while iron deficiency anemia can become severe and could lead to serious health problems, including high-output health failure and angina. Iron-deficiency anemia is described as one of the important complications experienced by patients underwent different types of bariatric surgery which could jeopardize the beneficial outcomes of these procedures. Therefore, we will conduct an observational study to assess the impact of sleeve gastrectomy on iron profile and to determine whether iron deficiency and anemia are complications of this procedure.

PROGRESS

On-going.

Project Title: Treatment of Corneal Cystine in Nephropathic Cystinosis by Topical 0.5% Cysteamine Eye Drops, RAC Proposal #: 2041-034.

Principal Investigator: Dr. Amal Al Hemidan

Co-Principal Investigator: Dr. Mohammed Alwaily , Dr. Abbas Al Abbad

PROJECT DESCRIPTION

This project is aiming of the treatment of patient with confirmed diagnosis of Cystinosis with local Cysteamine eye drops. Those patients are referred from the pediatric nephrology clinic after confirming their original disease. To date 25 patients have been enrolled in the study and follow-up of these patients is still on going.

PROGRESS

Patients have noticed remarkable improvement in symptoms. Patient who had severe photophobia have tremendously improved. However, signs "Crystal deposits in its cornea" continued to increase with the follow-up. We had few withdrawals from the study.

Final results are not completed yet.

Project Title: Infliximab Effects Compared to Conventional Therapy in the Management of Retinal Vasculitis in Behcet Disease, RAC Proposal #: 2021-079.

Principal Investigator: Dr. Amal Al Hemidan

Co-Principal Investigator: Dr. Khalid Tabbara

PROJECT DESCRIPTION

In this project the investigators aim was to compare the effect of treatment of Behcet Disease with use of anti human necrosis factor and (Infliximab) comparing to conventional therapy and follow-up the program, relapses and final outcome in both groups.

PROGRESS

Infliximab proved superior as far as treatment and final visual outcome of its group of patient.

This is a completed project. Data have been finalized and manuscript published in the American Journal of Ophthalmology, December 2008.

Project Title: External Pressure Compression for Umbilical Hernia Management in Infants: Randomized Clinical Trial, RAC Proposal #: 2071-070.

Principal Investigator: Dr. Saud Al Shanafey

PROJECT DESCRIPTION

External pressure compression use for umbilical hernia management is proven controversial. Despite its use by some people, evidence does not support its use. This is the first study designed to answer the question in a scientific way. Patients with umbilical hernia < 6m are randomized to either no intervention or external pressure compression groups. Both will be followed-up for 6 months to ascertain outcome.

PROGRESS

Still in a process of recruiting patients.

Project Title: Surgical Resident's Satisfaction with Current Surgical Training Program in Riyadh Area, RAC Proposal #: 2081-100.

Principal Investigator: Dr. Saud Al Shanafey

PROJECT DESCRIPTION

Surgical Resident's satisfaction with their training programs plays an important role in dictating its outcome. There were no previous reports to address this issue locally. This survey was conducted to explore surgical resident's satisfaction with their training programs in Riyadh area.

A survey questionnaire was designed to explore the view of surgical resident regarding many aspects of their training programs. The survey was distributed to all surgical residents rotating in 4 major hospitals in Riyadh area. The survey forms were distributed and collected by the authors directly from participating residents. Completed forms were then entered in a database. Frequency tables were generated for each question in the survey.

The survey was distributed to 78 surgical residents and 52 forms were retrieved (67%). Specialties included

General Surgery (64%), Orthopedic Surgery (13%), Neurosurgery (7%), Urology (7%), and Plastic Surgery (9%). While 45% of residents had comprehensive orientation on admission to the program, only 20% felt it was complete or helpful. 49% had an assigned mentor during training. Only 40% of residents felt that their trainer were committed to training, with consultants trained abroad more committed than those locally trained (62% vs 36%, p-value= 0.01). 88% want residents to be withdrawn from consultants who are not committed to training. 53% of residents felt that they are committed to their training, and 75% felt that other hospital staffs are not committed to their training. Only 38% felt that they are involved in planning their academic activities, and 84% felt that it did not meet their expectations. Only 15% felt they have enough bedside teaching or operative experience. Only 12% had their rotations' objectives emphasized to them, and although they felt they have enough evaluations (78%), 66% felt that these evaluations were low in quality and not helpful. 78% felt that current training does not meet their expectations, but 59% felt it was improving. 85% feels that external training better than local one, and 60% feels it should be mandatory. 87% acknowledged that Saudi residents may be committed to training externally than locally. While 90% felt that training programs should be unified nationally and controlled by one organization, only 65 feel that the current training council is capable of monitoring the training. 90% feel that there are significant differences in training among different institutions and only 28% feel that current reviews of programs by training council is effective.

These results show general dissatisfaction of surgical residents with their current training programs. It also emphasizes significant weakness of the current program and the ineffectivity of the current training council in monitoring it. We feel that a national review of surgical training programs is warranted in view of these results.

PROGRESS

Completed and submitted for publication.

Project Title: Wilms Tumor and Breast Feeding, RAC Proposal #: 2071-004.

Principal Investigator: Dr. Saud Al Shanafey

PROJECT DESCRIPTION

A study to check the association between Wilms tumor and Breast feeding.

PROGRESS

On-going. Data collected and now at the Analysis Phase.

Project Title: Laparoscopic Panceatotomy for Persistent Hyperinsulinemic Hypoglycemia of Infancy, RAC Proposal #: 2071-064.

Principal Investigator: Dr. Saud Al Shanafey

PROJECT DESCRIPTION

Case series.

PROGRESS

Completed and Accepted for publication in Journal of pediatric Surgery "in Press".

PUBLICATIONS

COLORECTAL SURGERY

- ↪ Uddin S, Hussain A, Ahmed M, Abubaker J, Al-Sanea N, AbdulJabbar A, Ashari L, Samar Alhomoud S, Al-Dayel F, Bavi P, Al-Kuraya K. Fatty Acid Synthase is a potential therapeutic target in microsatellite-unstable colorectal cancer. *Gastroenterology*. 2008 – IN PRESS.
- ↪ Bazarbashi S, El-Bassiouni M, Abdelsalam M, Soudy H, Sanea NA, Jabbar AA, Manji M, Fagih M, Ajarim D. A modern regimen of pre-operative concurrent chemo-radiation therapy in locally advanced rectal cancer. [Clinical Trial, Phase II. Journal Article. Research Support, Non-U.S. Gov't] *Journal of Surgical Oncology*. 98(3):167-74, 2008 Sep.
- ↪ Abubaker J, Bavi P, Al-Harbi S, Ibrahim M, Siraj AK, Al-Sanea N, Abduljabbar A, Ashari LH, Alhomoud S, Al-Dayel F, Uddin S, Al-Kuraya KS. Clinicopathological analysis of colorectal cancers with PIK3CA mutations in Middle Eastern population. [Journal Article] *Oncogene*. 27(25):3539-45, 2008 Jun 5.
- ↪ Uddin S, Ahmed M, Bavi P, El-Sayed R, Al-Sanea N, AbdulJabbar A, Ashari LH, Alhomoud S, Al-Dayel F, Hussain AR, Al-Kuraya KS. Bortezomib (Velcade) induces p27Kip1 expression through S-phase kinase protein 2 degradation in colorectal cancer. [Journal Article] *Cancer Research*. 68(9):3379-88, 2008 May 1.
- ↪ Al-Saleh I, Arif J, El-Doush I, Al-Sanea N, Jabbar AA, Billedo G, Shinwari N, Mashhour A, Mohamed G. Carcinogen DNA adducts and the risk of colon cancer: case-control study. [Journal Article. Research Support, Non-U.S. Gov't] *Biomarkers*. 13(2):201-16, 2008 Mar.
- ↪ Bavi PP, Abubaker JA, Jehan ZD, Al-Jomah NA, Siraj AK, Al-Harbi SR, Atizado VL, Abduljabbar AS, Alhomoud SJ, Ashari LH, Al-Dayel FH, Uddin S, Al-Kuraya KS, Al-Sanea NA. Colorectal carcinomas from Middle East. Molecular and tissue microarray analysis of genomic instability pathways. [see comment]. [Journal Article] *Saudi Medical Journal*. 29(1):75-80, 2008 Jan.

ENDOCRINE SURGERY

- ↪ Shahab Uddin, Abdul K, Siraj, Maha Al-Rasheed, Maqbool Ahmed, Rong Bu, Jeffrey N. Myers, Abdulrahman Al-Nuaim, Saif Al-Sobhi, Fouad Al-dayel, Prashant Bavi, Azhar R. Hussain, and Khawla S. Al-Kuraya. Fatty Acid Synthase and AKT Pathway Signaling in a Subset of Papillary Thyroid Cancers. *J Clin Endocrinol Metab*. October 2008, 93(10):4088-4097.
- ↪ Raef H, Alfadhli E, Al-Hajjaj A, Malabu U, Al-Sobhi S, Rifai A, Al Nuaim, A. High Rate of Persistent/Recurrent Disease Among Patients with Differentiated Thyroid Cancer in Saudi Arabia: Factors Affecting Non-Remission. *Annals of Saudi Medicine* 28(4) July-August 2008, pp. 227-281, www.saudiannals.net.
- ↪ Safwat A, Bissada N, Seyam R, Al Sobhi S, Hanash K. Clinical Spectrum of Pheochromocytoma: Analysis of 115 Patients. Submitted for publication. *British Journal of Urology*.
- ↪ Safwat A, Bissada N, Seyam R, Al Sobhi S, Hanash K, Jackson R. Pheochromocytoma in Children: A Clinical Spectrum. Submitted for publication. *Journal of Urology*.

- ↪ Bissada N, Safwat A, Seyam R, Al Sobhi S, Hanash K. Familial Pheochromocytoma. Submitted for publication. *Urologic Oncology*.

GENERAL MIS

- ↪ Hakeam Al Hakeam, Patrick O'Regan, Abdelrahman Salem, Fahad Bamehriz, Lina Jomaa. Inhibition of C-Reactive Protein in Morbidly Obese Patients after Laparoscopic Sleeve Gastrectomy. *Obes Surg*, DOI 10.1007/s11695-008-9729-y, 23 September 2008.

OPHTHALMOLOGY SURGERY

- ↪ Khalid F. Tabbara, Amr Nassar, Syed Osman Ahmed, Fahad Al Mohareb, Mahmoud Arjuf. Acquisition of Vernal and Atopic Keratoconjunctivitis Following Bone Marrow Transplantation. *American Journal of Ophthalmology* 2008; 146:462-465.

PEDIATRIC SURGERY

- ↪ Nasr A.A., Al-Mathami A., Al-Hathal N., Fadin A., Habib Z. Combined Spinal and Epidural Anesthesia in a Child with Epidermolysis Bullosa. *Pediatric Anesthesia* 2008, 18, 1211-1281.
- ↪ Habib Z., Awan M., Kolar M. Laparoscopic Duodenoduodenostomy in a Newborn with Situs Inversus Totalis. *Journal of Laparoendoscopic & Advanced Surgical Techniques*, August 01, 2008, 18(14): 654-656.
- ↪ Saud Al Shanafey, John Harvey. Long gap esophageal atresia: An Australian experience. *Journal of Pediatric Surgery*.

RENAL TRANSPLANT SURGERY

- ↪ Sirolimus Induced Dyslipidemia in Tacrolimus Based vs. Tacrolimus Free Immunosuppressive Regimens in Renal Transplant Recipients. Hakeam A. Hakeam, Ahmed H. Al Jedai, Syed M. Raza, Khaled Hamawi. *Ann Transplant*, 2008; 13(2): 46-53.
- ↪ D. Rabah, N. Al Hathal, T. Al Fuhaid, S. Raza, F. Al Yami, W. Al Taweel, M. Al Omar and N. Al Nagshabandi. Computed Tomography Angiogram: Accuracy in Renal Surgery. *International Journal of Urology*. October 2008: 1-3.

ORAL PRESENTATIONS

PEDIATRIC SURGERY

- ↪ Al Shanafey S. Morgagni Diaphragmatic in Children: Experience at Once Center, Oral Presentation at the 21st Congression of Asian Association of Pediatric Surgeons (AAPS 2008 Congress), 16-19 November 2008, Pullman Bangkok King Power Hotel, Bangkok Thailand.
- ↪ Al Shanafey S. The Transanastomatic Feeding Tube: A Useful Tool, Oral Presentation at the 21st Congression of Asian Association of Pediatric Surgeons (AAPS 2008 Congress), 16-19 November 2008, Pullman Bangkok King Power Hotel, Bangkok Thailand.
- ↪ Al Shanafey S. Laparoscopic Nissen Fundoplication for Patients Weighing less than 5kg, Oral Presentation at the 21st Congression of Asian Association of Pediatric Surgeons (AAPS 2008 Congress), 16-19 November 2008, Pullman Bangkok King Power Hotel, Bangkok Thailand.
- ↪ Al Nassar S. Minimal Invasive Surgery for Pediatric pathology, Oral Presentation at the 21st Congression of Asian Association of Pediatric Surgeons (AAPS 2008 Congress), 16-19 November 2008, Pullman Bangkok King Power Hotel, Bangkok Thailand.
- ↪ Al Nassar S. Synchronous Bilateral Wilms's tumor Single Institution Experience, Oral Presentation at the 21st Congression of Asian Association of Pediatric Surgeons (AAPS 2008 Congress), 16-19 November 2008, Pullman Bangkok King Power Hotel, Bangkok Thailand.

ABSTRACTS

ENDOCRINE SURGERY

- ↪ Al Otaibi N, Al Sobhi S, Al Zahrani N, "Outcome of Minimally Invasive Video-Assisted Parathyroidectomy vs Open Parathyroidectomy for Solitary Parathyroid Adenoma in KFSH&RC," 8th Annual Surgical Research & Residents Day, King Faisal Specialist Hospital & Research Centre, Marriott Hotel, 25 December 2008.
- ↪ Raef H., AlFadhi E., Al-Hajjaj A., Malabu U., Al Sobhi S., Rifai A., Al-Nuaim A., High Rate of Persistent/ Recurrent Disease among Patients with Differentiated

Thyroid Cancer in Saudi Arabia: Factors Affecting Non-Remission, *Annals of Saudi Medicine* 2008, 28(4): pp 277 – 281.

THORACIC SURGERY

- ↪ Al Kattan K. Plasmapheresis before Thymectomy in Myasthenia Gravis: Routine vs Selective Protocols. European Annual Thoracic Meeting, *European Journal Cardiothoracic Surgery*, March 2009; Vol 35: 392-397.
- ↪ Al Kattan K. Clinical Use of Combine positron Emission Tomography and Computer tomography in Recurrence of Thymoma. American Society of Thoracic Surgery. (It was presented and Accepted but not yet published. In-process for final review) as per Dr. Bawab.

WORKSHOPS AND SYMPOSIA

1. Saudi Colorectal Surgery Forum held on 22-26 March 2008.
2. Reconstructive & Anesthetic Breast Surgery Workshop held on 8-9 April 2008.
3. King Faisal Endovascular Therapy Workshop held on 18-19 October 2008.
4. 8th Annual Surgical Research & Residents Day, 25 December 2008

EDUCATIONAL ACTIVITIES

COLORECTAL SURGERY

1. Training of Surgery Residents in Bowel Anastomosis
 - ↪ Dr. A. Abduljabbar, Dr. P O'Regan

PLASTIC SURGERY

2. Microsurgery Training
 - On-going Weekly Activity for Residents Training
 - ↪ Dr. A. AlMalaq

VASCULAR SURGERY

3. Training of Vascular Residents on Suturing Techniques
 - On-going Weekly Activity for Residents Training
 - ↪ Dr. N. AlEnazi

LETTER TO EDITOR

- Tabasum Akram, Alaa Abduljabbar, Zakaria Habib, Saif Al Sobhi. Morbidity and Mortality Rounds in a Saudi Hospital, *Saudi Med J* 2008; Vol 29(11): 155-156

FUTURE RESEARCH DIRECTION

The Department will continue to enhance commitment to research activities, especially among our junior staff so that they can build their career on solid foundation, clinical knowledge and evidence-based medicine.

For next year, we aim to accomplish the following:

- Mandate residents to initiate research proposals at beginning of the year, to be supervised and precept by a consultant, for submission and presentation in the Annual Surgical Research Day held at the end of the year.
- In the process of submission to RAC for approval:
 - ↪ Margin Evaluation Post Excisional Biopsy of Breast Cancer, Investigator: Dr. M. Al Fehaily
 - ↪ Saudi Optical Coherence Tomography for Saudi Diabetic Macular Edema Study, Investigator: Dr. S. Al Hazzaa, Dr. F. Al Qahtani, Dr. A Al Hemidan
 - ↪ The incidence of Hirschprung's disease in the Riyadh area. Collaboration with national Guard Hospital, Principal Investigator: Dr. Stanly Crankson, (Consultant Pediatric Surgery, National Guard Hospital). Co-Principal Investigator: Dr. Zakaria Habib, (Consultant Pediatric Surgery, KFSH&RC).
 - ↪ The incidence of associated anomalies with anorectal malformation (ARM) in the Riyadh area. Collaboration with National Guard Hospital, Principal Investigator: Dr. Stanly Crankson, (Consultant Pediatric Surgery, National Guard Hospital). Co-Principal Investigator: Dr. Zakaria Habib, (Consultant Pediatric Surgery, KFSH&RC).

- ∞ The incidence of Pyloric stenosis in Riyadh area. Collaboration with National Guard Hospital, Principal Investigator: Dr. Mohammed Al-Rajhi, (Fellow Pediatric Surgery, National Guard Hospital). Co-Principal Investigator: Dr. Saud Al Shanafey, (Consultant Pediatric Surgery, KFSH&RC).
- ∞ Written versus Verbal Information in Consenting for Thyroidectomy: Patient Satisfaction & Information Retention (for RAC approval), Investigators: Hammami M., Al Sobhi S., Atalla S., Al-Zahrani A.
- ∞ The Role of Frozen Section in Detecting Metastatic Lymph Node (for RAC approval), Investigators: Al Hefdhhi, A, Al Sobhi S.
- ∞ Outcome of Minimally Invasive Video-Assisted Parathyroidectomy vs Open Parathyroidectomy for Solitary Parathyroid Adenoma in KFSH&RC (for RAC submission), Investigators: Al Zahrani, N, Al Otaibi, N, Al Sobhi S.

This Annual Report has been compiled and edited by the

OFFICE OF RESEARCH AFFAIRS

Layout and cover design by the

SCIENTIFIC INFORMATION OFFICE



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

Research Centre