KFSH&RC
RESEARCH REPORT
2009

The

KFSH&RC RESEARCH REPORT

2009

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:

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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

Research is an important component of this fine institution, and when combined with education and integrated clinical practice, we can achieve excellent standards of care.

As we reflect on our research accomplishments in 2009, there are compelling reasons to feel proud.

First, in terms of our research output, we produce quality . Our average impact factor is the highest when compared to the rest of the academic, medical, and research institutions within the Kingdom. In fact, we have consistently led in this category since they started monitoring publications statistics in the Kingdom. In addition to our high impact factors, our scientific publications are cited more often. Based on the latest figure, our citation rate is more than double the national average.

Second, we have enduring collaborative ties with world-renowned institutions. These collaborations ensure the cultivation of new and ground-breaking ideas; the very same ideas that get translated into innovative technologies and medical breakthroughs. It's worth mentioning that we also have a growing number of technical and scientific staff that are currently involved in fellowship programs with our partner institutions. Thanks to collaboration, they will be coming back here armed with a wealth of knowledge to help us enhance our capacity.

Third, we are getting the validation for our impact and contribution to the national initiative on science and technology. As proof, the amount of support we are getting from the government is very encouraging. For example, we have received a pledge of 500 million Saudi Riyals in support of cutting-edge research for the next five years. I am confident that this pledge is only the beginning for bigger and better things in the future.

And finally, we are being recognized for our excellence. As a testament to our excellence, one of our senior scientists, Dr. Khawla Al-Kuraya, who heads the Human Cancer Genome Research in CCC, recently received the King Abdulaziz Medal for her contributions in the field of research. This is the highest form of recognition that can be awarded to a civilian in the Kingdom.

In closing, I would like to extend my congratulations to all of you.

Qasim Al Qasabi, MD, FRCSI, FACS
Chief Executive Officer
King Faisal Specialist Hospital and Research Centre

OPENING REMARKS FROM THE EXECUTIVE DIRECTOR OF THE RESEARCH CENTRE

I remember the 1999 annual research presentations like it was yesterday. It did not go without a hitch. Coming up with a perfect three-day format and ensuring that presenters receive equal chances to impress us with their accomplishments and research contributions did not come easy. Pleading with the staff to sit through what many misguided participants thought of as boring presentations became a recurring task throughout the festivities. Through it all though, it was a success (the resulting first annual research report is a testament to that). We have effectively set a good precedent for future annual research presentations. More importantly, we have set a good measuring stick through which the success of future annual research presentations can be judged.

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

As I witness year after year of annual research presentations, I have noticed that the festivities and the presentation formats have not changed much. More encouragingly, the high spirits remain the same, if not better. Of course, problems still remain. Like before, we still struggle to please the presenters with the schedule of presentations. And like before, we still struggle to put bodies in the Prince Salman Auditorium to sit through what many misguided participants still regard as boring presentations. I personally would not call these excellent presentations boring (but then again I am known for my politeness).

In all seriousness, the way these activities are presented has not changed. The format in which the annual research report book (like the one you are holding now) is published every year has not changed. What has changed, however, is the quality of the research work being presented. They are timely, more practical, and actually better. In addition, you will notice that the majority of the research activities being presented now are more evidence-based. I have examined this phenomenon closely and have come up with a number of explanations why this is the case. It is possible that the shift to evidence-based research is caused by our growing reputation in the scientific community -- the pressure to protect that reputation and to stick to what has worked best in the past. The other explanation is that common sense dictates that the shift to evidence-based research enables the use of proven methodologies and the use of resources more judiciously and more effectively (i.e., the effective use of resources means that we can conduct more research using minimum resources). But no matter how carefully I examine this new trend, I cannot ignore the obvious: We have grown. We are showing signs of maturity. We have become more responsible.

In all my years of serving this institution as Executive Director of the Research Centre, I have never been more proud and confident in our work than today. Thank you for the great work and the responsible research.

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The

Research Centre

Report

The Department of

BIOLOGICAL AND MEDICAL RESEARCH

Biological and Medical Research

During the year 2009, the Biological and Medical Research Department continued its programs to further the development of scientific achievements in research in a diversity of fields, including but not limited to allergy and aerobiology, breast cancer, cell biology (diabetes and cardiovascular diseases), DNA repair and apoptosis, environmental health, laser medicine, molecular virology and infectious diseases. In addition to equipment in each area, communal equipment are available in the department for use including confocal microscopy, Sorvall centrifuge, ultracentrifuge, freeze dry systems, x-ray film processor, dionized water system, autoclaving, cold room and freeze room. 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 continuously provides 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.

Our scientists will elaborate on their research activities and findings in the subsequent sections that follow.

Major achievements for the year include:

- Casuarina tree pollen was identified as a probable cause of respiratory distress for “Dahran Project”.
- Using microarray in identification of age-specific signatures and molecular characterization of breast cancer progress in Saudi females.
- Examined the effects of dietary high Fructose Corn Syrup and Monosodium Glutamate on hepatic and visceral fat gene expression (Obesity Journal, NPG publishing group).
- Curcumin enhances the killing efficiency of nontoxic doses of cisplatin and γ-rays, which are widely used for the treatment of medulloblastoma patients.
- Finding the hepatitis C virus quasispecies that influence the treatment progress.
- Elucidation of the molecular mechanism of drug-resistance of Plasmodium falciparum, the causative agent of human malaria isolated from Saudi Arabia.

ACTING CHAIRMAN

Futwan Al-Mohanna, PhD, FIBiol, FRSC

ADMINISTRATIVE SUPPORT STAFF

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Allergy and Medical Aerobiology

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

Amaranthus (pigweed) is an allergenic weed shedding pollen in the air throughout the year in Saudi Arabia with peaks in autumn months. There are a number of *Amaranthus* species in Saudi Arabia. However, the dominant species on the ground and frequently encountered pollen in the air belongs to *Amaranthus viridis* 1 (*Av*).

Despite this fact, either Av is not included in the diagnostic profile in Saudi Arabia or commercial extract of other *Amaranthus* sp is included. This may result in false negative test in those patients who are exposed to *A. viridis*. There appear to be limited cross reactivity between the weeds pollen allergy but no such cross-reactivity has been documented within Amaranths species.

In this project we have made attempt to study biochemical and immunochemical aspects of the *A. viridis* in relation to allergy and asthma in Saudi Arabia.

HEAD OF SECTION

Syed M. Hasnain, PhD, FACAAI, FAAAAI

STAFF MEMBERS

Halima Al-Sini, PhD
Abdulrahman Al Sobri
Mubarak Al Enezi
Al Anoud Al Qassim
Cheryl Mijares

RESEARCH PROJECTS

Project Title: Diagnostic and Therapeutic Impact of Indigenous and Commercial Pollen Extracts of Amaranthus Species.

RAC Project # 2050 029

Investigators: *Syed M. Hasnain, Abdelkarim A. Alaiya, Halima Al Sini, Al Anoud Al-Qassim, Mai Al-Mohanna, Mohamnmed O. Gad-El-Rab*

Project Description

- Airborne pollen grains from the weeds, and in particular *Amaranthus viridis (Av)* and *Amaranthus lividus (Al)* (slender or green amaranth), are the most prevalent in various parts of Saudi Arabia. It appears that all *Amaranthus* species are allergenic and potential cause of respiratory allergy. However, neither *Av/Al* extracts nor *Av/Al* raw pollen grains are commercially available for diagnostic or therapeutic purposes. Because of its abundance in the country, sensitization and characterization of *Av* was undertaken.
- *Amaranthus* pollen grains were collected and/or acquired from various sources. *Av* and *Al* were collected from indigenous sources while *A. palmeri*, *A. retroflexus*, *A. hybridus, A. tuberculatus* were acquired from Greer and *A. retroflexus*, *A. tamariscinus* were acquired from Allergon. The raw pollen from these species were defatted and extracted in buffered saline *PH* 8.1. Proteins were estimated using GeneQuant 1300. Protein patterns of eight different types of *Amaranthus* samples were analyzed using SDS-PAGE as well as two-dimensional polyacrylamide gel electrophoresis (2-DE). Global protein expression profile was evaluated by computer-assisted image analysis (PDQUEST).
- Marked qualitative and quantitative changes in protein expression patterns from 2 DE- and 1-D SDS-PAGE images were observed. The results indicate that there were variations in proteins in the extracts of *Amaranthus*. *Av* with 5 bands at 87, 37, 36, 33, 20, kDas while *A. tuberculatus* with 6 bands at 87, 36, 70, 40, 36, 26, 24, shared only two bands with *Av*. The *A. retroflexus* having 7 bands at 70, 40, 36, 32, 26, 24, 28, shared only one band with *Av. A. hybridus* with 3 bands only at 87, 70 40 shared two bands with *A. tuberculatus* but only one with *Av*. Interestingly, *A. palmeri* did not show any shared band with *Av*. The three proteins in *Av* were missing in all other *Amaranthus*. The expression levels of differentially expressed proteins was used successfully in clustering of serum samples from patients exposed to different *Amaranthus* species.
- There appear to be proteins diversity in six – major *Amaranthus* species and similarities in the two indigenous species. While the reactive and cross-reactive proteins between the indigenous and commercial species are being investigated, the available commercial extracts appear to have different protein profile and may not be fully relevant to this region for the diagnosis of inhalant allergy and any suggested or subsequent immunotherapy. Further characterization and validation of these protein spots is warranted to explore their usefulness as biomarkers for accurate diagnosis and prognostic monitoring of *Amaranthus* species world wide.

Project Progress

Preparation of extracts:

- The collected and commercially acquired pollen were defatted with excess of diethyl ether / n-butanol and treated with chilled acetone.
- Antigen was extracted from the defatted pollen with 1:10 weight per volume $(w/v)^2$ concentration. The extract was prepared in Phosphate Buffered Saline (10 mM PBS pH 8, at 4 0C for 72 hrs). Extract obtained was dialyzed (mol. Wt. cut limit 3500) exhaustively against 85% PBS, lyophilized and kept at –20°C and reconstituted when and as required. Extracts were sterilized using Millipor filters (0.45µm, 0.22µm).
- For the biochemical studies in 2D SDS-PAGE, Phenol extraction 3 protocol was used, with some modification, followed by methanolic ammonium acetate precipitation.
- Protein content of each extract was determined by Bradford 4 method.

Skin Prick Test:

- Patients who agreed to participate, signed a consent form as approved by the Research Advisory Council (RAC) of KFSH&RC.
- The Skin Prick Test (SPT) method was applied in this study. All patients were skin tested with locally prepared

(indigenous and commercial pollen) *Amaranthus* extracts as well as commercial *Amaranthus* extract. The vials were supplied to the Allergy clinic with coded numbers from 1 to 11. All procedures included a positive and negative control.

Sodium dodecyl sulphate polyacrylamide electrophoresis (SDS-PAGE):

- The procedure outlined by Laemmli [5] was followed.
- SDS-PAGE was carried out using 12% polyacrylamide gel containing 0.1% SDS in conjunction with tris-glycine buffer (0.025 M Tris, 0.2 M glycine, 0.1% SDS) using Mini Electrophoretic Apparatus(Bio Rad). Extracts with varying protein concentrations were used in loading. The gels were calibrated with marker proteins (Bio Rad). After destaining, the gels were scanned.
- Skin prick tests was applied on 10 patients with seven (7) different types of *Amaranthus* allergens as listed in table I. Blood sera from positively reacting patients were analyzed using two-dimensional polyacrylamide gel electrophoresis (2-DE).

Electrophoresis, scanning and image analysis:

- High-resolution two-dimensional gel electrophoresis (2-DE) was used to generate protein fingerprints from 5 serum samples from positively reactive patients to *Amaranthus* species. Gels were stained with silver nitrate and scanned using a laser densitometer. Data was analyzed using PDQUEST software (Bio-Rad).

Data preprocessing / Data analysis:

- Quantitative datasets from the PDQUEST gel analysis package match set was exported in the form of data table, with rows representing gels and columns representing spots. Variables were first selected using two different statistical methods [6, 7]. Data were log transformed to the base of 2 and datasets were normalized prior to analysis. The pre-processed data were analyzed by hierarchical clustering and corresponding analysis using the J Express software (java.sun.com).

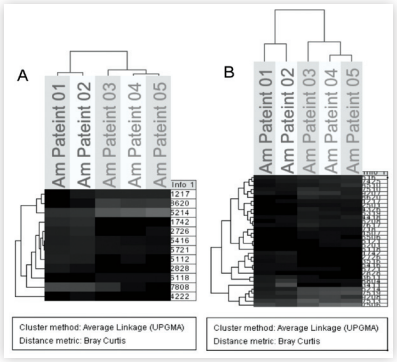
MOST IMPORTANT ACHIEVEMENTS

Protein expression patterns between different species of Amaranthus samples:

- The 1-D SDS-PAGE results revealed some variations in proteins within the extracts of *Amaranthus* species. *Av* displayed 5 bands at 87, 37, 36, 33, 20, kDas while *A. tuberculatus* displayed 6 bands at 87, 36, 70, 40, 36, 26, 24, and shared only two bands with *Av.* The *A. retroflexus* exhibited 7 bands at 70, 40, 36, 32, 26, 24, 28, and shared only one band with *Av. A. hybridus* showed 3 bands only at 87, 70 40 and shared two bands with *A. tuberculatus* but only one with *Av. A. palmeri* did not show any shared band with *Av.* The three proteins in *Av* were missing in all other *Amaranthus* species.
- Serum samples obtained from five patients inoculated with different types of *Amaranthus* were analyzed. Crude serum samples were prepared and analyzed by 2-DE for both qualitative and quantitative differences in the expression of multiple polypeptides. An average total number of 588 spots were resolved and approximately 94% of the resolved protein spots were successfully matched between all the gels.

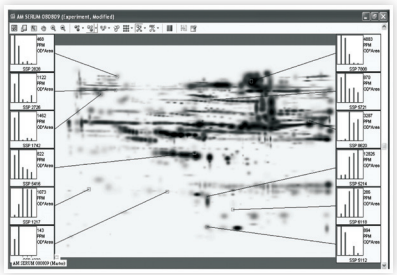
Global Protein Expression Profiling of Serum Samples:

- We have generated and characterized the expression of multiple proteins in human serum samples of patients exposed to 7 different types of *Amaranthus* allergens using the technique of two-dimensional gel electrophoresis (2-DE/PDQUEST). Sera were collected from patients diagnosed with allergic rhinitis or asthma and divided into two groups based on their skin prick test-reaction patterns. Two patients demonstrated similar high expression changes to *Amaranthus* # 5 & 6 allergens and were classified as group 1 while three samples showed low expression to *Amaranthus* # 5 & 6 and were referred to as group 2. We did not observe distinct reaction patterns among the 5 patients to the rest of the *Amaranthus* #1, 2, 3, 4 & 7 allergens.
- Changes in the expression of 12 proteins were observed between group 1 and group 2 samples. These differential changes were considered significant ($P < 0.05$ with 98%CI) using combined student's t test and more than 2-fold difference in the levels of expression of these protein spots. In addition 33 protein spots were differentially expressed between the two groups of samples using partial least square analysis.
- These 12 and 33 datasets of protein spots were used in the unsupervised hierarchical cluster analysis and the samples were correctly classified into two distinct groups (Figures 1A & 1B).
- The location and expression patterns of some of these



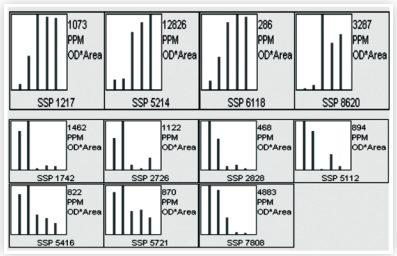
Patients 1 & 2 = Gp1 (Red) = High reaction to *Amaranthus* #5
Patients 3,4 & 5= Gp2 (Green) = Low reaction to *Amaranthus* #5

Figure 1. Hierarchical cluster analysis using the expression patterns of 12 (A) and 33 (B) protein datasets that are differentially expressed between the two groups of samples.



Patients 1 & 2 = Gp1 (Red) = High reaction to *Amaranthus* #5
Patients 3,4 & 5= Gp2 (Green) = Low reaction to *Amaranthus* #5

Figure 2. Global differential expression of some of the differentially expressed spots between serum samples from patient with different skin prick test reactions to *Amaranthus* allergens.



Patients 1 & 2 = Gp1 (Red) = High reaction to Amaranthus #5
Patients 3,4 & 5= Gp2 (Green) = Low reaction to Amaranthus #5

Figure 3A. Quantity Graphs of spots that differs significantly and at least 2-fold highly expressed in Gp2 than in Gp1 samples.
Figure 3B. Quantity Graphs of spots that differs significantly and at least 2-fold highly expressed in Gp1 than in Gp2 samples

proteins are shown in figure 2. Four of the 12 protein spots were at least more than 2-fold highly expressed in group 2 than group 1 samples, while 8 spots were up regulated in group 1 than in group 2 samples. The differential expressions of some of these proteins are shown as quantity graphs in Figure 3.

The species of *Amaranthus* in our country appear to be different than species of allergenic extracts available in the market. In the absence of a clear cross-reactivity between Av and commercially available extracts, we have worked to determine the allergenic differences, if any, between these species on our population. We used 2-DE to separate proteins from serum samples of allergy patients exposed to different *Amaranthus* pollen allergens. We have identified some protein spots on 2-DE gels that should be further validated in order to support their usefulness as potential *Amaranthus* biomarkers for the diagnosis and therapy monitoring of allergy patients. The project is in progress.

- Publication of four (4) collaborative manuscripts in the international journals and book.
- Submission of two (2) collaborative manuscripts in the international journals.
- Submission of three (3) technical reports to KACST (AR 27-11).
- Submission of Allergotek Appraisal report to RC administration.
- Installation of three (3) Burkard Volumetric Samplers at Dahran Project.
- Presentation of two (2) abstract at the World Allergy Congress.
- Presentation of two (2) abstracts including one at the American Academy of Allergy, Asthma and Immunology meeting in Washington.
- Presentation of two (2) invited lectures: one at the First Middle-East Asia Asthma Allergy Congress in Dubai and the second at Asthma and Clinical Immunology Symposium at KFSH&RC.
- Successful organization of the World Asthma Day (WAD) 2009 including presentation of a public lecture at Al-Mather Cave Park of the KFSH&RC, as a member of the Asthma Education Committee.
- Completion of writing and compilation of 2 manuscripts, 1 Guidebook, 1 booklet and 2 in the process.
- As an Editor-in-Chief, successful release of two APAWG (Asia-Pacific Aeroallergen Working Group) –

World Allergy Organization (WAO) newsletter (*www.worldallergy.org*).

- *http://www.worldallergy.org/esp/apawg_0109.pdf* -1st issue (January 2009)
- *http://www.worldallergy.org/enews/0709/APAWG_Newsletter2.pdf* - 2nd issue (July 2009)
- Publications of patient education articles in Arabic.
- Induction as a member of the Regional Advisory Committee of the World Allergy Organization International Scientific Conference. Asthma and Co-morbid Conditions, 6-8 December 2010. (www.worldallergy.org/2010dubai).

PUBLICATIONS

- HASNAIN, SM., KHAN, M., SALEEM, A., WAQAR, MA (2009): "Prevalence of Asthma and Allergic Rhinitis among School children of Karachi, Pakistan 2007". *Journal of Asthma and Allergy*. Volume 46, Pages 86-90.
- WAQAR, MA., KHAN, M., HASNAIN, SM. et al (2009): "Prevalence of Allergy and Asthma in School Children of Islamabad, Pakistan". *World Applied Sciences Journal*. Volume 6 (3), Pages 426-432.
- WAQAR, MA, KHAN, M., SALEEM, A., HASNAIN, S.M (2009): Possible Effects of Cultivated Plants in the Development of Allergy in Population of Sindh. Pak *J Chem Soc* 31 (2), 2009.
- WAQAR, M.A., KHAN, M., SALEEM, A., AKHTAR, T., KHASKHLI, A.A. AND HASNAIN, SM: Allergy and Asthma: Prevalence among the school going children in Pakistan. In: Science, Technology and Innovation for Sustainable Development in the Islamic World: The policies and politics rapprochements, Eds. A.S. Majali, M. Ergin and M. R. Zou'bi, *National Printing Press*, Amman, Jordan, 2008.

SUBMITTED MANUSCRIPT

- WAQAR, MA, HASNAIN SM., KHAN, M (2009): Airborne and Allergenic Pollen Grains of Karachi City using Volumetric Sampling. Aerobiologia (submitted).
- WAQAR, M.A., KHAN, M., HASNAIN, S.M., et al. Incidence and Severity of Allergic rhinitis, Asthma, Atopic eczema and related disorders in Islamabad. Allergy Asthma Proc. Submitted for publication.

TECHNICAL REPORTS

Submitted to KACST: ARP 27-11

- Isolation, purification and immunochemical characterization of allergenic protein(s) from *Amaranthus* viridis pollen grains. First Six Monthly Progress Report
- Isolation, purification and immunochemical characterization of allergenic protein(s) from *Amaranthus viridis* pollen grains. Annual Progress Report for the Full Year
- Isolation, purification and immunochemical characterization of allergenic protein(s) from *Amaranthus* viridis pollen grains. Progress Report for the First Half of the Second Year

Report to Research Centre Admin:

- Allergotek Diagnostic and Therapeutic Program – Appraisal Report

ABSTRACTS PUBLISHED

- HASNAIN, S.M, ALAIYA, A.A, AL-SINI, H. et al (2009): "Diagnostic and Therapeutic Impact of Indigenous and Commercial Pollen Extracts of *Amaranthus* Species". XXI World Allergy Congress, 06 – 10 December 2009, Buenos Aires, Argentina.
- HASNAIN, S.M, AL-FRAYH, A.R, GAD-EL-RAB, M.O (2009): "Pattern of Allergic Sensitization in Pediatric Population in Saudi Arabia". XXI World Allergy Congress, 06 – 10 December 2009, Buenos Aires, Argentina.
- KHAN M, HASNAIN SM., WAQAR MA: Allergy and Asthma in Pakistan: "Airborne Pollen Prevalence in City of Karachi, Pakistan" Presented at 35th all Pakistan Conference, Dr. Panjwani Centre for Molecular Medicine and Drug Research (PCMD), University of Karachi.
- HASNAIN SM., ALAIYA AA., GAD-EL-RAB, MO., AL-MOHANNA, MA. et al (2009): *Amaranthus* Pollen Extracts: Protein Diversity and Impact on Diagnosis – American Academy of Allergy Asthma and Immunology. March 13-17, 2009, Washington DC. Journal of Allergy and Clinical Immunology. Volume 123, Issue 2, Pages S160-S160, May 2009.
- HASNAIN SM., Allergens in the Middle-East and their clinical implications, EMEAAAIC Dubai, 26-29 March 2009.

MANUSCRIPT AND MANUAL IN PREPARATION

- HASNAIN SM et al: Prevalence of Asthma, allergic Rhinitis and Eczema and their etiologic factors in the Middle-East & Neighboring Countries.
- HASNAIN SM et al: Indigenous allergens in Saudi Arabia: Efficacy of Diagnostic Kits: A Multi-Centre Study in the Region.
- HASNAIN SM et al: Physician Guide for Aeroallergens in Saudi Arabia.
- HASNAIN SM et al: Common Inhalants and Food allergens with their scientific and Arabic names.
- HASNAIN S.M et al: Pattern of Asthma Admission 2004-2008 at KFSH&RC.
- HASNAIN S.M et al: Booklet for World Asthma Day 2010.

INVITED LECTURES

- Allergens in the Middle-East and their clinical implications, EMEAAAIC Dubai, 26-29 March 2009.
- Regional Pollen Allergen: Invited Lecture at Health Authority, Abu-Dhabi (HAAD), 9 April 2009.

PRESENTATIONS

Local

- "World Asthma Day 2009 – You can control your Asthma". Al-Mather Cave Park, King Faisal Specialist Hospital and Research Centre. 07 May 2009.
- "Epidemiology of Allergic Disease and Common Aeroallergens in Saudi Arabia". Allergy, Asthma & Clinical Immunology Symposium. 17 –18 November 2009, King Faisal Specialist Hospital and Research Centre, Riyadh

International

- *Amaranthus* Pollen Extracts: Protein Diversity and Impact on Diagnosis – American Academy of Allergy Asthma and Immunology (AAAAI), Annual Meeting, 13 – 17 March 2009, Washington, DC.
- Diagnostic and Therapeutic Impact of Indigenous and Commercial Pollen Extracts of *Amaranthus* Species. XXI World Allergy Congress, 06 – 10 December 2009, Buenos Aires, Argentina.
- Pattern of Allergic Sensitization in Pediatric Population in Saudi Arabia. XXI World Allergy Congress, 06 – 10 December 2009, Buenos Aires, Argentina

PROJECTS

- Allergotek Diagnostic and Therapeutic Program
- Isolation, purification and immunochemical characterization of allergenic protein(s) from *Amaranthus* viridis pollen grains. First Six Monthly Progress Report
- House Dust Mite (in preparation)

SANDSCRIPT

- HASNAIN, SM (2009) Successful Clinical Trial of Indigenous Allergens for Diagnostic and Therapeutic Use, Sand Script, Volume 33, Issue 31, February 2009.

Breast Cancer Research

Breast Cancer is the major cause of morbidity and mortality among females in Saudi Arabia. Clinical observations indicate that the breast cancer developed before the age 45 accounts for 45% of all female breast cancers in Saudi Arabia as compared to 9.6% in USA. Breast cancer in young Saudi females is more aggressive in nature with poor prognosis and disease free survival. Thus new diagnostics, prognostic and therapeutic markers are needed. It is also widely held that breast cancer initiates as the premalignant stage of atypical ductal hyperplasia (ADH), progresses into the preinvasive stage of ductal carcinoma *in situ* (DCIS), and culminates in the potentially lethal stage of invasive ductal carcinoma (IDC). Genome-wide microarray-based gene expression analysis would be expected to provide a new opportunity to discover genes specifically activated or inactivated during the course of breast cancer progression.

HEAD OF SECTION

Suad M. Bin Amer Al-Abdoullah, PhD

STAFF MEMBERS

Asmaa Nofal
Gina Gonzales

RESEARCH PROJECTS

Project Title: Identification of Environmental and Genetic Factors that Influence Breast Cancer Development and Therapy in Saudi Females.
RAC Project # 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.

Project 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. We compared mRNA expression in tumors in young (≤ 45 years) (n=35) to those arising in two mature groups: 45 to 55 (n=13); and older age ≥ 55 (n=25). Within the young women's subset, additional analyses were performed comparing women age younger than 35 years (very young) with those age 35 to 45 years. A multi-factor ANOVA was performed to determine significant differences in gene expression levels between different age groups. Significantly modulated genes were defined as those with absolute fold change > 2.0 and adjusted p-value < 0.05. Functional pathway, gene ontology and network analysis of tumor specific genes (up/down-regulated) were performed. We have identified 77 signature genes specific to tumor in young age (≤ 45). A subset of differentially expressed genes was validated using real-time RT-PCR. The enriched functional categories of young-age tumor signature genes include carcinogenesis, tissue development, cellular development, cellular growth and proliferation, tumor morphology, and cell death. The network analysis revealed potential critical regulatory role of PI3K/Akt, p38 MAPK, ERK/MAPK, NF-κB, MYC, and ERbB-2 in disease characteristic arising in younger women. Breast cancer appearing in young women represents distinct biological characteristics with unique deregulated signaling pathways that should be highlighted and applied in better diagnosis, prevention, and therapeutic options.

Project Title: Determination of the Role of Several Radio-Flourinated Bombesin Peptides as Molecular Imaging Agent for the Detection of Breast Cancer.
RAC Project # 2030058. In collaboration with Department of Cyclotron and Radiopharmaceuticals.
Investigators: *Suad Bint Mohamed Bin Amer and Ibrahim Al-Jamaz*

Project Descritpion

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

FUTURE RESEARCH DIRECTION

- We are in progress of examining 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. In addition, selected genes from these signature genes will be confirmed using immunohistochemistry.
- We will also perform immunohistochemistry to validate the signature genes identified for young group vs. older group peri-menopause and post-menopause of Saudi breast cancer patients
- The signature genes that are identified for Saudi breast cancer patients of young group (age < 45) with older group peri-menopause and post-menopause will be compared 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.
- Further gene profiling analysis will be performed on clinical characterization based on different factors for newly collected breast cancer samples.

Cell Biology

Latest figures reveal a 24% prevalence of Type 2 Diabetes (T2D) in the Saudi population. 60% of Saudi Cardiovascular patients suffer from Diabetes. Diabetes is a progressive disease proceeded by hypertriglyceridemia, hyperglycemia, impaired glucose tolerance and central adiposity. We have previously hypothesized that there are 3 major changes to the human diet since the 1970's, which may have contributed to the rise in obesity and T2D: (1) the increase in free fructose consumption in the form of High Fructose Corn Syrup; (2) Trans-hydrogenation of dietary fat.(3) The use of the food flavor enhancer Monosodium Glutamate. Our Diabetes Program consists of seven main projects which can been summarized by 4 full-length original articles published this year: [1] Dietary trans-fat combined with monosodium glutamate induces dyslipidemia and impairs spatial memory. *Physiol Behav. Epub* 2009 Nov 27. [2] Diabetes of the liver: the link between Nonalcoholic Fatty Liver Disease & HFCS-55. *Obesity* (Silver Spring) 2009 Mar 12. [3] Effect of Dietary Monosodium Glutamate on Trans Fat-induced Nonalcoholic Fatty Liver Disease. *J Lipid Res*. 2009 Aug;50(8):1521-37. (4) Sugar-Sweetened Carbonated Beverage consumption correlates with BMI, waist circumference, and poor dietary choices in school children. BMC Public Health, in print.

HEAD OF SECTION

Futwan A Al-Mohanna, PhD, FIBiol, FRSC
Kate S Collison, PhD

DIABETES RESEARCH STAFF

Soad Saleh
Angela Inglis
Nadine Makhool
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Rhea Mondreal
Rana Al-Rabiah

DIABETES RESEARCH STAFF

Ranjit Parhar, PhD
Reem Al-Hejailan
Mohammed Kunhi
Qammar Al Haffar

RESEARCH PROJECTS

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

2 manuscripts published: *J. Lipid Res* 2009; 50(8):1521-37 [Epub ahead of print . Nov 11. 2008]; *Obesity* (Silver Spring). 2010 Jan 28. [Epub ahead of print]

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 Project # 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

1 manuscript published: *BMC Public Health*, Epub April 2010.

Project Title: Metabolic studies into the etiology of Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Hepatic Steatosis (NASH).
RAC Project # 2070 006
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

1 manuscript published; *Obesity* (Silver Spring) 2009 17, 2003-2013 [Epub ahead of print Mar 12.].

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

1 manuscript published; *Physiol Behav.* 2010 Mar 3;99(3):334-42. Epub 2009 Nov 27.

Project Title: Vaccinia Virus Complement Control Protein (VCP): Potential to Prevent Damage to Xenoreactive Cells.
RAC Project # 2050 046
Investigators: *Collison, K; Saleh S, & 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

Manuscript in preparation.

PUBLICATIONS

- Effect of dietary monosodium glutamate on trans fat-induced nonalcoholic fatty liver disease. Collison KS, Maqbool Z, Saleh SM, Inglis A, Makhoul NJ, Bakheet R, Al-Johi M, Al-Rabiah R, Zaidi MZ, Al-Mohanna FA. *J. Lipid Res* 2009; 50(8):1521-37
- Diabetes of the Liver: The Link Between Nonalcoholic Fatty Liver Disease and HFCS-55. Collison KS, Saleh SM, Bakheet RH, Al-Rabiah RK, Inglis AL, Makhoul NJ, Maqbool ZM, Zaidi MZ, Al-Johi MA, Al-Mohanna FA. *Obesity* (Silver Spring) 2009 17, 2003-2013 [Epub ahead of print Mar 12.].
- Dietary trans-fat combined with monosodium glutamate induces dyslipidemia and impairs spatial memory. Collison KS, Makhoul NJ, Inglis A, Al-Johi M, Zaidi MZ, Maqbool Z, Saleh SM, Bakheet R, Mondreal R, Al-Rabiah R, Shoukri M, Milgram NW, Al-Mohanna FA. *Physiol Behav*. 2010 Mar 3;99(3):334-42. Epub 2009 Nov 27.
- Effect of Dietary Monosodium Glutamate on HFCS-Induced Hepatic Steatosis: Expression Profiles in the Liver and Visceral Fat. Collison KS, Maqbool ZM, Inglis AI, Makhoul NJ, Saleh SM, Bakheet RH, Al-Johi MA, Al-Rabiah RK, Zaidi MZ, Al-Mohanna FA. *Obesity* (Silver Spring). 2010 Jan 28. [Epub ahead of print]
- Aberrant BRAF splicing as an alternative mechanism for oncogenic B-Raf activation in thyroid carcinoma. Baitei EY, Zou M, Al-Mohanna F, Collison K, Alzahrani AS, Farid NR, Meyer B, Shi Y. *J Pathol*. 2009 Apr;217(5):707-15
- RNase L downmodulation of the RNA-binding protein, HuR, and cellular growth. Al-Ahmadi W, Al-Haj L, Al-Mohanna FA, Silverman RH, Khabar KS. *Oncogene*. 2009 Mar 2. [Epub ahead of print]
- Mutations in C2orf37, encoding a nucleolar protein, cause hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal syndrome. 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. *Am J Hum Genet*. 2008 Dec;83(6):684-91. Epub 2008 Nov 20.
- Radioiodinated naphthylalanine derivatives targeting pancreatic beta cells in normal and nonobese diabetic mice.Amartey JK, Shi Y, Al-Jammaz I, Esguerra C, Al-Otaibi B, Al-Mohanna F. *Exp Diabetes Res*. 2008;:371716.

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 of carcinogenesis 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 effective anti-medulloblastoma agent, it enhances the effect of both cisplatin and γ-rays.
- We have also shown that the tumor suppressor protein p16 is a major regulator of functional cross-talk between breast cancer cells and their stromal fibroblasts.
- We have also found that the frequency of p53 mutations is among the highest in the world (40 %), and we have shown that 72% of the Saudi breast cancer patients whose tumors harbor p53 mutations are less than 50 years old.
- We have identified 7 new mutations in p53 in breast cancer tumors from Saudi patients.

HEAD OF SECTION

Abdelilah Aboussekhra, PhD

STAFF MEMBERS

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RESEARCH PROJECTS

Project Title: Cellular and Molecular Characterization of Medulloblastoma in Saudi Patients: Correlation With Prognosis and Therapy.

RAC Project # 2050016

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

Project Description

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

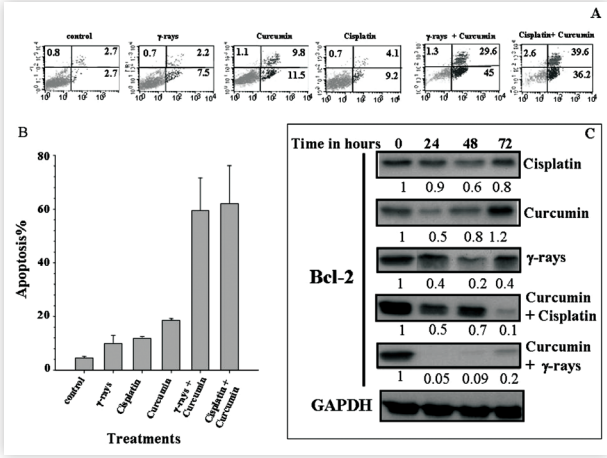

Figure 1. Curcumin potentiates the effect of cisplatin and γ-rays in inducing apoptosis in medulloblastoma cells. A. AnnexinV/PI-Flow cytometry, B. Histogram, C.Western blot.

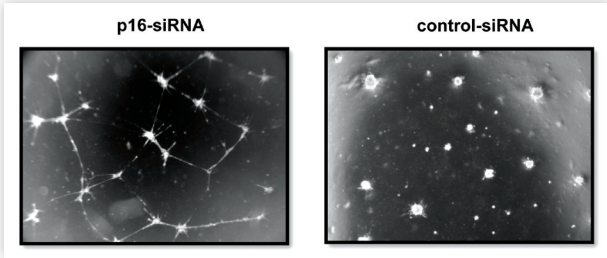

Figure 2.

Progress

We have also shown this year that curcumin enhances the killing efficiency of nontoxic doses of cisplatin (widely used as chemotherapeutic gent) and γ-rays (essential for the treatment of medulloblastomas). In addition, we present clear evidence that piperine, an enhancer of curcumin bioavailability in humans, potentiates the apoptotic effect of curcumin against medulloblastoma cells. This effect was mediated through strong down-regulation of Bcl-2. These results indicate that curcumin, a natural non-toxic compound, represents great promise as therapeutic agent against medulloblastomas.

Project Title: Investigation of the Role of Stromal Fibroblasts in the Development of Breast Carcinoma: The Tumor Suppressor p16INK4A Protein as Target.

RAC Project # 2080009

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

Project Description

In the present proposal we are aiming at elucidating the functional interplay between stromal fibroblasts and breast carcinoma. More precisely we will study the role of the tumor suppressor p16 in the stromal-tumor interaction. To this end we are planning to investigate p16

expression level in Carcinomas-Associated Fibroblasts (CAFs) and their corresponding Tumor Counterparts Fibroblasts (TCFs) from the same patient. Furthermore, we are also planning to study the effect of p16 down-regulation, using p16 siRNA, on the molecular and cellular features of breast stromal fibroblast cells and on the proliferation of breast carcinomas. The resulting data will provide new insights into the importance of breast stromal fibroblasts in the development and treatment of carcinomas and the active involvement of p16 in this complex phenomenon.

Progress

We have first shown that in most cases the level of p16 is lower in CAFs as compared to their adjacent TCFs and normal breast fibroblasts (NBFs), in addition, the p16 expression is also low in more than 40% TCFs as compared to NBFs. These data present the first indication that, like in cancer cells, p16 level is also reduced in stromal fibroblasts. We have also shown that the down-regulation of p16 changes the 3D shape and enhances the invasiveness of breast stromal fibroblasts into matrigel, which is an *in vitro* mimic of the basement membrane (Figure 2).

Project Title: Gene-Environment Interaction: TP53 Gene Mutation Spectrum in Breast Cancer in Saudi Arabia.

KACST/RAC Project Number # 2040037

Investigators: *A. Aboussekhra (PI), Nujoud Al-Yousef, A. Tolbah, T. Twigery, O. Al-Malik, D. Ajareem, Adhar Al-Sayed, Adnan Ezzat*

Project Description

Owing to the important role of the *TP53* gene in tumor suppression, we analyzed in this project the possible link between *TP53* mutations and SNPs with the early onset of breast cancer in Saudi females by direct sequencing of the *TP53* gene (exons 4 to 9) in breast cancer tissues.

Progress

We have found that the prevalence of TP53 mutations in breast cancer Saudi patients is among the highest is the world (40%). Interestingly, 73% of the patients whose tumors harbored p53 mutations were under 50 years of age. Furthermore, we have identified 7 novel mutations and 16 mutations that have never been identified in breast cancer tissues. Intriguingly, all the novel mutations were in exon 4, which is a hotspot for p53 mutations for the breast cancer Saudi population. Furthermore, we have found excess of G:C→A:T transitions at non-CpG sites, suggesting a high exposure of the patients to N-nitroso compounds. In addition to p53 mutations we have shown that the RR form of codon 72 polymorphism represents a potential risk factor, while RP form represents a protection factor against breast cancer among the Saudi females. Moreover, we have shown that the SNP72 is strongly associated with early onset of breast cancer in the Saudi population.

FUTURE RESEARCH DIRECTION

Further elucidate the molecular mechanisms that govern the functional interplay between breast carcinomas and their adjacent stromal fibroblasts and the role of this interaction in cancer development and therapy. To this end, we will continue looking for the important factors and pathways that control this interaction. We are also interested in the identification of agents with the ability to normalize the stromal fibroblasts and their effects on epithelial cells. Furthermore, we would like to study the effect of aging on these fibroblasts and their interaction with epithelial cells.

PUBLICATIONS

- Maha H. Elamin, Zakia Shinwari, Siti-Faujiah Hendrayani, Hindi Al-Hindi, Essam Al-Shail, Yasser khafaga, Amani Al-kofide and Abdelilah Aboussekhra. Curcumin inhibits the Sonic Hedgehog signaling pathway and triggers apoptosis in medulloblastoma cells. (2010) *Mol. Carcinogenesis*. 49:302-14.
- Nisreen M. Al-Moghrabi, Ibtehaj S. Al-Sharif and Abdelilah Aboussekhra. The RAD9-dependent gene transactivation is required for excision repair of active genes but not for repair of non-transcribed DNA (2009) *Mutation Research*, 663:60-68.

Environmental Health Servivces

The Environmental Health Section (EHS) continues to maintain its primary goal to assess environmental pollutants that have potential impact on the health of general population with a particular emphasis on children and women. The 2009-year was marked by a surge of our fund support. We obtained the approval of King Abdulaziz City for Science and Technology (KACST) for the following project: ***"Mercury exposure during lactation and its effects on Saudi infant's neurodevelopment"*** under the 29th Annual Grant Program. The aim is to evaluate postnatal exposure to different forms of organic and inorganic mercury and its association with delayed neurological development at different age groups. It is anticipated that this research project will provide relevant data to public health authorities concerned with pediatric environmental health hazards that can be used in developing prevention and control programs. Our ultimate goal is to influence the professional view with the important role of environmental factors in health and disease, inform public health policy and promote public awareness. This report overviews briefly the progress of our research projects over the last year.

HEAD OF SECTION

Iman Al-Saleh, PhD

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Neptune Shinwari
Ammar Al-Sabbahen
Reem Al-Rouqi
Rola Elkhatib
Cecilia Angela Obsum

RESEARCH PROJECTS

Completed Projects

Project Title: Effects of Environmental Pollutants Exposure on the Pregnancy Outcome of Women in Al-Kharj Area.

RAC Project # 2040 017

This project was 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.

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

Summary of the results

This cross sectional study was designed to test the hypothesis that *in utero* exposure to pollutants such as heavy metals, DDT and polycyclic aromatic hydrocarbons adversely affects fetal growth and development. A total of 1578 women participated in this study. The total sample reached 6312 samples consisting of cord blood, maternal blood, placental tissue and urine samples. Lead, cadmium and mercury were measured in cord, maternal and placental tissues by Atomic Absorption Spectrophotometer digesting samples with acid. Based on the Commission of the German Federal Environmental Agency (CGFEA) reference values for lead in children and women, 12.8% and 2.3% of cord and maternal blood had lead >3.5 and 7µg/dL respectively. Lead in cord and maternal blood samples were correlated confirming its placental transfer that leads to an early fetal lead burden. Approximately 9.3% of our participants had high placental lead levels above the 95th percentile in the range of 0.83 to 78µg/g dry wt. Cadmium was detected in 94.8% and 97.9% of cord and maternal blood samples, only 5 newborns had cadmium above the American Occupational Safety and Health Administration (OSHA) threshold limit of 5µg/L. When we based our results on the newly revised children reference value set by the CGFEA, we found all our newborn's cord blood samples had cadmium levels >0.2µg/L and 48.6% of mothers had blood cadmium >1.0µg/L. As shown in other studies, we observed no correlation between cord and maternal cadmium levels. This suggests that the placenta restricts the transfer of cadmium between mother and fetus. However, placental cadmium levels in our participants were higher than in other reported countries. Approximately 87.5% and 48.7% of cord and maternal blood had mercury >0.8µg/L and 2.0µg/L, the CGFEA reference values. Though mercury levels were higher in cord than maternal but they were correlated indicating its placental transfer. Around 50% of the women had placental mercury in the range of 0.031-13.00µg/g dry wt which is much higher than other countries. After controlling for confounders, both linear and logistic regression models showed that cadmium had effect on many outcomes such as delivery complications, birth weight, Small for gestational age (SGA), head circumference, gestational age, placental thickness and placental diameter. This is quite disturbing because cadmium is cumulative metal and exposure at early age should be limited as much as possible to prevent serious health effects such as nephrotoxicity and/or osteoporosis which manifest at older age. Lead had a negative impact on birth weight, SGA and cord length. These are indicators of its possible adverse effects on the growth and development later in life as proved in other studies. In the case of mercury exposure, it had an impact on head circumference, crown head length, birth weight, placental diameter, cord length and ponderal index. Our results suggest that a substantial proportion of the newborns are at risk of deleterious mercury neurotoxic effects during a lifetime.

Our results also showed that the main metabolites detected in cord and maternal blood was *p,p'*-DDE reflecting past exposure. These analytes were measured by Gas Chromatography coupled with Electron Capture Detector. About 51.1% of our newborns had cord *p,p'*-DDE >0.2µg/L, a limit that showed significant effect on the cognitive functions of child at the age of 4 years. Though, cord and maternal *p,p'*-DDE were highly correlated, it was higher in cord than its counterpart maternal blood. Detection of all metabolites in placenta is an indication of DDT and its metabolites transfer to the fetus. DDT and its metabolites had negative effect on head circumference, crown head length, placental weight,

placental thickness, cord length and SGA. Our finding is quite important taking into consideration recent studies on the impact of *in utero* organochlinated pesticides exposure on neurodevelopment during childhood or/and early adulthood.

Though, we found many predicators of pollutants in this study; there is an urgent need to conduct environmental studies in order to specify possible sources of exposure.

Among the studied oxidative DNA damage biomarkers, maloanoaldehyde was the best predicator for many pregnancy outcomes such as crown head length, birth weight, placental weight, cord length, cord diameter, delivery complications and SGA. Urinary cotinine levels were as only associated with SGA, while urinary 1-hydroxypyrene was related to crown head length and placental diameter. These findings suggest that strategies of preventing and reducing oxidative stress or smoking in pregnant women have the potential to benefit fetal growth.

In conclusion, our results confirm that exposure of pregnant women to these pollutants may pose a threat to the fetus as well as other adverse health consequences. It is important to introduce precautionary measures to eliminate or minimize unnecessary risk of the fetus to these pollutants, which could be predisposes to susceptibility to adult diseases in later years. We are hoping that these evidences may be considered in the decision making process to establish guidelines to protect or guide women against exposure to pollutants during and before pregnancy.

The final report was submitted to KACST on 13th of October 2009. One abstract was presentation at the "49th Annual Society of Toxicology Meeting and ToxExpo", which was held in Salt Lake City, Utah, USA, from 7-11 March, 2010. One manuscript has already been submitted to peer-reviewed journal for publication.

Ongoing Research Projects

Project Title: Saudi Children and Mercury Exposure: the Impact of Dental Amalgam.

RAC Project # 2070 010

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.

Investigators: *Iman Al-Saleh (Principal Investigator), Al Anoud Al-Sudairi (a master student) and Ebtesam Al Olyan (Co-Investigator)*

Project Description

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

Progress

The analytical part of this project was completed and the student is still working on data analysis and finalizing her master thesis.

Project Title: Determination of Phthalates in Drinking Water,Juices and Milk Packed in Locally Manufactured Plastic Bottles.

RAC Project # 206 0028

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 and we requested a 10 months extension due to technical problems.

Investigator: *Iman Al-Saleh.*

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

During this year, we managed purchase and install the CombiPAL Autosampler with Headspace Solid and Liquid Phase Microextraction to the Agilent Gas Chromatography/Mass Spectrometer. The analyses of DEHP, DBP, DINP, DIDP and BBP in 10 various brands of locally manufactured apple and orange juices were completed. We are in the process of analyzing the same compounds in milk and water samples.

CORE SERVICE ACTIVITIES

We managed to complete the analysis of 1372 organic and inorganic analytes in environmental samples of water, soil and vegetations for private environmental firm as part of our ongoing service-for-fee activities.

FUTURE RESEARCH DIRECTION

The EHS will continue working on our existing and newly approved projects. 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. Health implications of mercury exposure in children. *International Journal of Environmental & Health* 2009; 3(1): 22-56.
- Al-Saleh I, Shinwari N, Al-Enazi S. Assessment of lead in cosmetics products. *Regulatory Toxicology & Pharmacology* 2009; 54: 105-113.
- Al-Saleh I, Shinwari N, Al-Amodi M. Accumulation of mercury in ovaries of mice after the application of skin-lightening creams. *Biological Trace Element Research* 2009; 131(1): 43-54.
- Al-Saleh I, Coskun S, El-Doush I, Billedo G, Mashhour A, Jaroudi K, Al-Shahrani A, Al-Kabra M, Mohamed G. Outcome of *in-vitro* fertilization treatment and DDT levels in serum and follicular fluid. *Medical Science Monitor* 2009; 15 (11): BR320-333.
- Al-Saleh I, Nester M, Mashhour A, Moncari L, Shinwari N, Mohamed G, Rabah A. Prenatal and postnatal lead exposure and early cognitive development: Longitudinal study in Saudi Arabia. *Journal of Environmental Pathology, Toxicology and Oncology* 2009; 28(4):283-302.

Laser Medicine

Low Power Laser Therapy (LPLT) is recognized worldwide for its importance in Dentistry, Dermato-logy, 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 eradi-cating tumors with the help of photosentizisers.

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 SECTION

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

STAFF MEMBERS

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Bernard L. Andres, RMT (AMT)
Azizah A. Al-Anazi, BSc (Biochem)
Joan R. Chico

RESEARCH PROJECTS

Project Title: Photo-Biostimulation: Laser Effect in Wound Healing of Diabetic and Non Diabetic Rats.
RAC Project # 2020002
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 Project # 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.

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. Thus, the laser continues to be an important tool in clinical patient care and of the application of laser in the new millennium for the benefit of human kind.

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

PUBLICATIONS

Book Chapter

- 4th Book in "Laser Medicine, Dentistry, Surgery and Veterinary Trilogy Updates" Zlatko Simunovic et.al. eds (2009) "PHOTOBIOSTIMULATION: The Effect of Various Lasers in Non-Diabetic and Diabetic Wound and Burns", Pp. 179 – 215. Farouk A. H. Al-Watban, MSc, PhD, FASLMS, Bernard L. Andres, RMT, Xing Yang Zhang, MD and Azizah A. Al-Anazi, BSc.

Full Manuscripts

- Al-Watban, F.A.H. Zhang, XY, Andres, BL and Al-Anazi, A. AB "Visible Lasers were Better than Invisible Lasers in Accelerating Burn Healing on Diabetic Rats", *Photomedicine and Laser Surgery*, April 2009, Vol. 27, No. 2 pp. 269-272.
- Al-Watban, F.A.H. "Laser Therapy Converts Diabetic Wound Healing to Normal Healing", *Photomedicine and Laser Surgery*, February 2009, Vol. 27. No. 1, pp. 127-135.
- Al-Watban F.A.H., Andres BL (Paper 2008). "Low Power Laser Therapy for Wound and Burn Healing", *Arab Health* 2008, The Official Magazine of the Arab Health Exhibition, Issue 3, 2008, pp 48-51.
- Al-Watban F.A.H., Zhang XY, Andres BL, Al-Anazi AAB (Paper 2008). "Visible Lasers Were Better Than Invisible Lasers in Acceleration Burn Healing on Diabetic Rats", *Photomedicine and Laser Surgery*, Vol. 26, N0. 5, 2008, pp. 10-16.
- Al-Watban F.A.H., Zhang XY, Andres BL, Al-Anazi AAB (Paper 2008). "The Significance of Treatment Parameters Using Various Photon Sources in Normal and Diabetic Wound and Burn Healing", Invited Paper, *WALT* 2008 – 7th International Congress Proceedings, 19-22 October 2008, Sun City, South Africa.

Abstracts

- F.A. H. Al-Watban, Laser Concepts in Health Care Workshop, "The Difference between Laser Therapy & Laser Surgery", International Conference on Radiation Medicine: Clinical Applications and Innovative Approaches, KFSH&RC, Riyadh, KSA, March 01 - 04, 2010.
- F. A.H. Al-Watban "Low Power Laser Therapy of Non-Diabetic and Diabetic Wounds and Burns", International Conference on Radiation Medicine: Clinical Applications and Innovative Approaches in KFSH&RC, Riyadh, KSA, March 01 - 04, 2010
- F. A.H. Al-Watban, B.L. Andres, X.Y. Zhang and A. A. Al-Anazi, "Cosmetic Effect of LPLT As A Wound And Burn Healer", GCC Derma 2009 Conference in Doha, Qatar, December 16 - 20, 2009
- F. A.H. Al-Watban, B.L. Andres, X.Y. Zhang and A. A. Al-Anazi, "Wound & Burn Healing for Diabetics using Low Power Laser Therapy in Comparison with other Modality", NESA Days 2009 in Athens, Greece, May 28 - 30, 2009
- F.A.H. Al-Watban, X.Y. Zhang, B.L. Andres and A. A. Al-Anazi, "Low Power Laser Therapy for Burns and Wound Care", EMLA Congress 2009 in Prague, Czech Republic, May 20 - 23, 2009
- F. A.H. Al-Watban "Laser Therapy Converts Wound & Burn Diabetic Healing to Normal Healing: 893 Rats were used in this research" *PMLS* 2008 Volume 27 Number 1, 2009 pp 127-135.

- F.A.H. Al-Watban,, X.Y Zhang, B.L. Andres, A.A. Al-Anazi (Paper) "Visible Lasers Were Better Than Invisible Lasers in Acceleration Burn Healing on Diabetic Rats" *PMLS* Vol. 26, No. 5 pp. 10-16.
- F.A.H. Al-Watban, B.L. Andres And X.Y.Zhang "The Cosmetic Efficiency Of Laser Therapy For Wound & Burn Healing" International congress in Aesthetic, anti-Aging Medicine & Medical Spa Middle East in Dubai, UAE, November 29-December 01, 2008.
- F.A.H. Al-Watban, "The World Acade,y for Laser Applications (WALA) Its activities, Present & Future Plans". Presented at the 29th Annual Meeting of Japan Society for Laser Surgery & Medicine (JSLSM) 15-16 November, 2008 at Tokyo, Japan.
- F.A.H. Al-Watban, B.L. Andres and X.Y.Zhang "Cosmetic Effect Of Lpl Therapy On Wound & Burn Healing". Presented at the 29th Annual Meeting of Japan Society for Laser Surgery & Medicine (JSLSM) 15-16 November, 2008 at Tokyo, Japan.
- F.A.H. Al-Watban, B.L. Andres and X.Y.Zhang, "The Effect Of LPL Therapy On The Cosmetics Of Burn And Wound Healing In Diabetic Rats" presented at the Dubai Congress on anti-Aging Medicine (DCAAAM) on November 7-9, 2008 at Dubai, UAE.
- Farouk A.H. Al-Watban, PhD "LASER SCIENCE AND TECHNOLOGY IN BIOMEDICINE FOR THE ARAB WORLD" Proceedings the 5th Congress of Scientific Research Outlook in the Arab World-Scientific Innovation and Sustained Development 26-30 October at Fez, Morocco.
- F.A.H. Al-Watban,, X.Y Zhang, B.L. Andres, A.A. Al-Anazi (Abstract) "The Application of Low Power Laser in Accelarating 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 at Helsinki, Finland
- B.L. Andres, F.A.H. Al-Watban, XingYang Zhang (Abstract) "Comparison of 633nm Diode Laser Therapy, Regranex and Solcoseryl in Diabetic Burn Healing: Biochemical and Biomechanical Analysis of Scar". Proceedings the 7th International Congress of World Association for Laser Therapy (WALT 2008) 19-22 October 2008 at Sun City, South Africa.
- XingYang Zhang, F.A.H. Al-Watban, B.L. Andres (Abstract) "The Changes of Tumor Volume and Weight after PDT: An Animal Study". Proceedings of the 7th International congress of World association for Laser therapy (WALT 2008) 19-22 October 2008 at Sun City, South Africa.
- F.A.H. Al-Watban,, X.Y Zhang, B.L. Andres, A.A. Al-Anazi (Abstract) "Cosmetic Effect of Low Power Diode Laser (670 Nm) Light On The Healing of Burns" for the 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, B.L. Andres, X.Y Zhang, A.A. Al-Anazi (Abstract) "Modification of Scar Tissue Morphology Using Low Power Diode Laser (670 Nm) On Burn Healing" for the 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 (Full Paper) "The Significance of Treatment Parameters Using Various Photon sources in Normal and Diabetic Wound and Burn Healing" for the Proceedings of the 7th International Congress of World Association for Laser Therapy (WALT 2008) 19-22 October 2008 at Sun City, South Africa.

OTHER ACTIVITIES

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

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

Immediate goals

- To support Medical Professionals, Engineers, Scientists and End-Users of Laser Technology for training, Education, Research and Technical aspects of this rapidly advancing industry.

- To collaborate with manufacturers and end-users for systems and product development.
- To serve as an agency aiding in certification programs for laser professionals; Laser Safety Officers and Laser Operators.
- To serve as one stop resource centre for continuous education, year round local and international seminars, workshops and symposia.

Long term goals

- To encourage relocation of selected photonics/opto-electronics industries in the GCC Countries as partners in application based development of laser systems.
- To organize and conduct laser product expositions as a strategy for market expansion and to foster cooperation.

WALA ACTIVITIES DURING 2009

- "Laser Concepts in Healthcare" Workshop, March 4, 2010, International Conference on Radiation Medicine: Clinical Applications and Innovative Approaches held at KFSH&RC, Riyadh, Saudi Arabia organized by WALA (World Academy for Laser Applications) in collaboration with the Biomedical Physics Department.
- Invited Speaker - Laser Concepts in Healthcare Workshop "The Difference between Laser Therapy and Laser Surgery" and LPL Therapy of Non-Diabetic and Diabetic Wounds and Burns at the International Conference on Radiation Medicine organized by the Biomedical Physics Department of KFSH&RC in Riyadh, Saudi Arabia, March 1–4, 2010.

Molecular Virology and Infectious Diseases

Diseases caused by infectious organisms continue to be a major cause of morbidity and mortality worldwide. Human movements, emergence of drug-resistant strains, and inadequate health care services are important factors that contribute to the persistence of such diseases. Also, some of these diseases are common in under-developed countries that do not have the means to develop research to find new drugs or vaccines against the causative agents of these diseases.

MVID unit concentrates on studying the distribution and prevalence of infectious agents in the Kingdom. Molecular techniques are employed to study viral and bacterial genomic variations and genotypes. Our major effort in this direction was on human hepatitis viruses, human papilloma virus and other bacteria that cause nosocomial infections including *Acinetobacter sp.*, vancomycin-resistant *enterococci*, and methicillin-resistant *Staphylococcus aureaus*. 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 SECTION

Ahmed A. S. Al-Qahtani, PhD

STAFF MEMBERS

Mohammed N. Al-Ahdal, PhD
Alwaleed Alaidan, PhD
Abdulrahman Al-Suwaine, PhD (*transferred to Allergy section - 10 February 2010)*
Abdulrahman Abukhdeir, PhD
Damian Dela Cruz, DVM
Suhair Abu-Zaid, MSc
Marie Fe Bohol
Mashael al-Enazi
Nisreen Khalaf
Hannan Shaarawi

SIGNIFICANT ACHIEVEMENTS

- Molecular typing of swine influenza virus (H1N1).
- Finding the hepatitis C virus quasispecies that influence the treatment progress.
- Establishing new technologies for DNA fingerprinting of bacterial isolates.
- Elucidation of the molecular mechanism of drug-resistance of Plasmodium falciparum, the causative agent of human malaria isolated from Saudi Arabia.
- Training of students on molecular techniques in microbiology.
- Three full proposals were presented to KACST for fund for year 2010 as follows:
  - Molecular genetic analysis of Hepatitis C Virus (HCV) in relation to resistance to treatment.
    Principal Investigator: Ahmed Al-Qahtani, PhD (MVID)Co-Investigatores: 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
  - Prevalence of human papillomavirus genotypes among Saudi females in Aseer Region (Saudi Arabia) and its involvement in cervical epithelial neoplasia.
    Principal Investigator: Mohammed N. Al-Ahdal, PhD (MVID)
    Co-Investigators: Ahmed Al-Qahtani, PhD (MVID), Mona Al-Mushait, MD, King Khalid University, Abha, Dr. Saad Dajem, PhD, King Khalid University, Mohamed Shoukri, PhD, BESC, KFSHRC).
    Proposed fund: 2,332,000 Saudi Riyals.
  - Evaluation and modeling of the cervical cancer genome post-HPV infection among Saudis: Molecular Targets for New Therapies.
    Principal Investigator: Abdelrahmman Abukhdeir, PhD (MVID)
    Co-Investigators: Ahmed Al-Qahtani, PhD (MVID), Mohammed N. Al-Ahdal, PhD (MVID), Hanif Khalak, (Genetics), Bedri Karakas, PhD (BMR), Tarfah Muammar, MD (Family medicine), Namik Kaya, PhD (Genetics), Dilek Colak, PhD, (genetics).
    Proposed fund: 1,500,000 Saudi Riyals.

The Department of

BIOSTATISTICS, EPIDEMIOLOGY, AND SCIENTIFIC COMPUTING

Biostatistics, Epidemiology, and Scientific Computing

"We are what we repeatedly do. Excellence, then, is not an act, but habit."

-Aristotle

The Biostatistics, Epidemiology and Scientific Computing (BESC) Department has been and will remain distinctive for its commitment to support the rigorous scientific programs of the Research Centre, enriched by the availability of challenging national research agenda for the new millennium. We believe that this commitment will reflect a deeply held conviction that both pursuit of knowledge and translation of research to benefit the health of the people. Consistent with its mission the BESC takes pride in having good relationships with a diverse range of clinical, research and educational institutions, and the government.

CHAIRMAN

Mohamed Shoukri, PhD

ADMINISTRATIVE STAFF

Alia Gabr
Cielo Dupaya Mendiola
Ismail El Sayed Mohamed
Abel Pangilinan

ACHIEVEMENTS

The year 2009 was a year of many significant achievements for the BESC Department. In summary, the BESC:

- Obtained approval by KACST, PSCDR and KSU to fund the National Research project: "*The Saudi National Mental Health Survey*". This project is a collaboration with Prince Salman Center for Disability Research, Ministry of Health, Ministry of Economy and Planning, King Saud University, Harvard University, and the University of Michigan.
- Produced three cumulative disease registry reports. One for the GCC cancer registry for the years 1998-2005 another for the Cleft Lip Palate and Craniofacial Anomalies for the years 1999-2008, and the third is for the CHD for the years 1998-2008.
- Continued to maintain the RC servers up and running with 0% downtime (excluding the scheduled power shutdown).
- Maintain the NLNBS network links to the LIMS server for smooth processing of the blood samples.
- Designed and developed several web based application the most important of which are:
  - Development, launching, and completing of the web-applications and the By-Laws for National Family Safety Registry. (http://www.nfspreg.org.sa).
  - Design, development and launching of the Financial Management & Accounting System (RC administration).
  - Design and Development of database for The National Comprehensive plan for Science & Technology.
- Design and launching of BLOGS for the websites of:
  - National Medical & Health Research Strategy
  - Saudi Congenital Heart Defects Registry
  - Financial Management & Accounting System for the Research Centre (*http://rc.kfshrc.edu.sa/fmas/*)

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.

HEAD OF UNIT

Mohamed Shoukri, PhD

STAFF MEMBERS

Naser El Kum, PhD *(until June 2009)*
Dilek Colak, PhD
Salah Al Gain, MSc
Abdelmoneim Eldali, MSc
Samia Abu Al Hashim, BSc
Wilhelmina Ventura, BSc

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.

RESEARCH PROJECTS

Project Title: Homogeneity Testing of Twin Concordance: Score Tests, Confidence Interval and Sample Size Requirements.
RAC Project # 209007
Investigator: *M.M. Shoukri*

Project Description

Evaluating the influence of genetic factors on the variability of traits is a subject of great interest to genetic epidemiologists. The biometrical approach to assessing the degree of clustering of quantitative traits has traditionally relied on measures of correlations among family members, with the success in this regard linked to the use of the well-developed normal theory. When the traits of interest are measured on a binary scale, such as presence or absence of disease condition, a useful way to gather information regarding the influence of genes on the distribution of the trait is to compare the concordance rates for monozygotic (MZ) and dizygotic (DZ) twins. Smith argued that any differences occurring between individuals of an MZ twin pair must be attributable to environmental factors, since they are genetically identical. Furthermore, if it is justified to assume that the environmental variability within pairs is the same for both types of twins, then the extent of the excess in the MZ correlation relative to the DZ correlation may reflect the strength of the genetic influence on the variability of the trait.

For rare traits, it is recognized that there are problems associated with the ascertainment of affected individuals. To overcome this problem, it is usual to base the inference on the proband concordance rate (CR). This is defined as the proportion of co-twins with the trait for affected individuals independently ascertained. This definition is simple, and leads to an estimate of concordance which is independent of the ascertained probability.

Objectives

1. For two independent samples, we compare the concordance rates in a sample of MZ twins to that in an independent sample of DZ twins using the likelihood-based WALD and Score tests.
2. Evaluate the coverage probabilities of the confidence interval on the difference between two concordance rates using Monte-Carlo simulations.
3. Applying the methods to two data sets; drinking habits in twins asthma and hay fever published data.

Progress

We have formed the multilevel likelihood function and estimated the model parameters. Furthermore the Asymptotic variances of the parameters have been obtained by inverting the Fisher's information matrix. Simulations and estimation from published data will be done in the next few months.

Project Title: Likelihood Inference on the Relative Risk in Split-Cluster Designs.
RAC Project # 2090030
Investigators: *Mohamed M. Shoukri and Dilek Colak*

Project Description

Split-cluster experiments are widely used by investigators in health sciences when naturally occurring aggregate of individuals with nested subgroups may be assigned to different interventions. Cited examples include the split

mouth trials, in which a subject's mouth is divided into two segments that are randomly assigned to different treatment groups. When the response variable of interest is binary, statistical methods developed to evaluate the effect of interventions depended on non-parametric methods. These methods are simple to apply, but are known to be less efficient. In this proposal, we propose to establish a full likelihood inference procedure and develop a score test on the significance of the relative risk as a population effect size.

Objectives

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

Progress

We have constructed the split design bivariate distribution for the binary responses. The Feiler's method and the Wald's large samples confidence intervals have been derived. Comparison between the methods in terms of efficiency (width of interval) show that the Wald's approach is better when the RR is near the edge of the parameter space. However, when the sample size is large, both techniques give comparable results.

Project Title: Modeling Familial Co-aggregation of Congenital Heart Defects: An exploratory Data Analysis From the CHD Registry.

RAC Project # 2070021

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

Project Description

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 project, 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.

Progress

A paper has been accepted for publication in The International Journal of Biostatistics.

Project Title: Establishing Equivalence of Two Treatments Using Neyman's C (α) Test,
RAC Project # 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 " 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: Hunting for One of the Autism Genes That Might Be Linked to Osteopetrosis With Renal Tubular Acidosis.
RAC Project # 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. Multiple manuscripts are under preparation.

Project Title: Molecular Characterization of Autism Spectrum Diseases: A Pilot Study for Three Distinct Disorders. RAC Project # 2040 024.
Investigators: *Kaya N, Colak D, Al-Odaib A, Demirkaya O, Sakati N*

Project Description

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

Progress

We have performed gene expression profiling using Affymetrix's Human HG-U133 Plus 2.0 gene expression chips on whole blood RNA from patients and sex and age matching controls. We have identified significantly altered genes that are common among the autism spectrum diseases. The Principle Components analysis as well as hierarchical clustering clearly classified individuals based on their genetic etiology. Functional and pathway analysis have been performed. 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 Project # 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. Mutation analysis has been performed on the collected samples.

Project Title: Proteomic analysis of human breast cancer stem cells/progenitor cells.
RAC Project # 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

We are in the process of collecting samples. Preliminary analysis has been performed on the collected samples.

Project Title: Identification of Environmental and Genetic Factors that Influence Breast Cancer Development and Therapy in Saudi Females.
RAC Project # 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 45 accounts for 45% of all female breast cancers in Saudi Arabia as compared with only 9.6% in USA. Breast cancer in young Saudi females is more aggressive in nature with poor prognosis and disease free survival. Thus new diagnostics, prognostic and therapeutic markers are needed. We conducted a comprehensive analysis of global gene expression changes to characterize the underlying biological mechanisms of young age breast cancer in Saudi Arabia. We also investigated gene expression profiles of cancer progression from normal to pre-invasive stage of ductal carcinoma *in situ* (DCIS) and to potentially lethal stage of invasive ductal carcinoma (IDC).

Progress

We analyzed the whole-genome mRNA expression profile from tumor and adjacent disease free tissues of 115 samples using Affymetrix GeneChip Human Genome U133 Plus 2.0 Arrays. Both unsupervised and supervised analyses were performed. We have identified 77 signature genes specific to tumor in young age (≤ 45). A subset of differentially expressed genes was validated using real-time RT-PCR. Functional and pathway analysis revealed some distinct and shared functional categories and pathways among three age subgroups. The enriched functional categories of young-age tumor signature genes include carcinogenesis, tissue development, cellular development, cellular growth and proliferation, tumor morphology, and cell death. Our 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. Breast cancer appearing in young women represents distinct biological characteristics with unique deregulated signaling pathways. One manuscript is under preparation, and presented at local and international conferences.

Project Title: Positional Cloning of Genes Underlying Genetics Disorders With Prominent Neuro-Developmental Manifestations in Several Extended Families.
(RAC Project # 2060 035)
Investigator: *D. Colak*

Progress

Samples from ten families were collected, and linkage analysis and targeted sequencing of the genes in the linkage region were performed.

Project Title: Genomics, Transcriptomics, and Proteomics Analysis of Ovarian Hyperstimulation Syndrome: A Comprehensive Molecular Look to a Complex Syndrome.
RAC Project # 2100 002)
Investigators: *M Dagestani, N Kaya, D Colak, S Coskun, NA AlEissa, MH Daghestani, KA Awartani*

Project Description

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

Progress

This project has been recently approved by KSU-KACST Joint Grants Support for Center of Excellence, and under review with RAC.

Project Title: Wound Infection Rate and Risk Factors in Colorectal Surgery Patients at KFSH&RC-Riyadh Saudi Arabia.
RAC Project # 2041071.
Primary Investigator: *Denise Hibbert*
BRU Investigator: *Abdelmoneim Eldali, Wilhelmina Ventura*

Project Description

To identify an accurate wound infection rate after colorectal surgery and the associated risk factors in this patient population at KFSH&RC in Riyadh, Saudi Arabia. The study will cover all adult patients, at KFSH&RC, undergoing colorectal surgery, for which an abdominal incision is planned.

Progress

Data analysis completed.

Project Title: Determination of the Cutoff Value of Cytomegalovirus (CMV) Viral Load that is Indicative of Infection in Hematopoetic Stem Cell Transplant Patients.
RAC #: 2081 085
Primary Investigator: *Jameela Edathodu, MD*
BRU Investigator: *Abdelmoneim Eldali*

Project Description

Cytomegalovirus (CMV) infection and disease is a major cause of mortality and morbidity in hematopoetic stem cell transplant (HSCT) recipients. The incidence of this has considerably reduced since the introduction of preemptive therapy with ganciclovir or foscanet. At KFSH&RC we utilize the CMV pp65 antigenemia to monitor for CMV infection, which is not highly sensitive. The development of CMV PCR assays have now been shown to be more sensitive and efficient in diagnosing CMV infection. This test was recently introduced in our laboratory but is not being utilized as much as it should be because a cutoff value that indicates CMV infection has not been determined. To utilize cutoff values from other labs is not possible as each lab uses different levels.

Progress

In the data collection phase.

Project Title: Second Allogeneic Stem Cell Transplantation in Pediatric Patients at KFSH&RC.
RAC Project # 2081 098
Primary Investigator: *Mouhab Ayas, MD*
BRU Investigator: *Abdelmoneim Eldali*

Project Description

Second SCT is now considered a viable option for patients in whom the first SCT was unsuccessful. The two conditions that merit consideration for a second SCT are either graft failure (primary or secondary) or disease relapse in malignant disorders (with or without graft failure). In the literature, there is now an increasing wealth of data available on second SCT particularly in patients with relapsed leukemia and some studies have even explored the value of reduced intensity conditioning in such patients. This is a retrospective analysis of a cohort of strictly pediatric patients who underwent second stem transplantation for non-malignant disorders at the same institution. In this study, we will try to identify the different factors that may affect the ultimate outcome.

Progress

Data Analysis Completed. A paper has been published.

Project Title: Impact of Laparoscopic Sleeve Gastrectomy on Iron Level and the Incidence of Iron-Deficiency Anemia.
RAC Project # 2071 047
Primary Investigator: *Hakeam A. Hakeam, MD*
BRU Investigator: *Abdelmoneim Eldali*

Project Description

Laparoscopic sleeve gastrectomy (LSG) has been recently introduced as a stand-alone, restrictive bariatric surgery. Theoretically, LSG attenuates micronutrients deficiencies and associated complications that typically observed

following malabsorptive procedures. This is a prospective, cohort study of the patients who will undergo LSG. The aim of this study is to assess iron indices and the 1-year incidence of iron deficiency in patients undergoing LSG. Preoperative hemoglobin and iron indices including serum iron, transferring saturation, ferritin, and soluble transferrin receptor will be compared before and after surgery.

Progress

Data analysis completed. A paper resulted from this project.

Project Title: Long Term Treatment of Congenital Pseudoarthrosos of Tibia (CPT), and Intramedullary Fixation. RAC Project # 2091 069.
Primary Investigator: Zayed Al-Zayed, MD
BRU Investigator: Abdelmoneim Eldali

Project Description

Congenital Pseudoarthrosis of the Tibia (CPT) is a rare disease which has different modalities of treatment. The abnormal bowed bone that fractures and heals with abnormal tissue which makes it difficult to treat. Spontaneous union occurs in 3%, so the best way to treat it is through surgery and it has high association with neurofibromatosis. After union there is still residual deformities, and has high incidence of refracture. KFSH&RC opted to treat it with resection and intramedullary fixation. This retrospective study will assess the method of fixation, union rate and residual deformities of the affected leg.

Progress

In the data collection phase.

Project Title: A Study to Examine the Concordance Between the Neuropsychology Data and the EEG, PET, and MRI Findings in the Pre-Surgery Evaluation of Epilepsy Patients.
RAC Project # 2061 080
Primary Investigator: *Dr Ahmed M. Hassan*
Co-Primary Investigator: *Dr Abdulaziz Al-Semari, Dr Mona Al-Khawajah*
BRU Investigator: *Wilhelmina Ventura*

Project Description

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

Progress

Data for 189 cases have been collected and entered into an SPSS database. P.I. completing missing information.

Project Title: Study of Demographic, Clinical, Pathological, Management, and Outcome Characteristics of Thyroid Cancer at KFSH & RC: A Retrospective Study.
RAC Project # 2071 071, BESC # 009/2008
Primary Investigator: *Ali Alzahrani, MD*
Co-Primary Investigator: *Saud Al-Harthi, MD, Mohamed Al-Harthi, MD, Gamal Mohamed, PhD*
BRU Investigator: *Wilhelmina Ventura*

Project Description

The vast majority of patients with thyroid cancer are referred to KFSH &RC. Once managed at their initial presentation, patients remain on a life-long follow-up due to the high recurrence rate even after many years of initial diagnosis. Based on the well-maintained tumor

registry of KFSH & RC, the number of patients referred annually has been gradually increasing. But, because of the excellent prognosis in the vast majority of patients, a large pool of patients are still alive and on follow up either in remission or having persistent/recurrent disease. Currently around 3,000 thyroid cancer patients are on long-term follow-up at KFSH &RC. The hospital continue to receive about 150-200 new cases every year. This large pool of patients provides an excellent opportunity for the study of the disease in all its aspects. A number of studies on the disease profile have been published from KFSH & RC but, was published around 10 years ago.

Since then several changes and evolutions took place in the diagnosis and management of thyroid cancer. The standard of care has become much more uniform matching international standards. With this background we strongly feel that it is time to review our data for the purpose of research and education. We will study a representative sample of patients for their demographic and clinical characteristics, diagnostic work-up, initial and follow-up management and outcome.

Progress

Data for 356 patients seen in 1998 and 1999 have been collected and entered into an SPSS database. About 20 more cases to be added. P.I. conducted preliminary analysis.

Project Title: Gulf Center for Cancer Registration.
RAC Project # 2061 022, BESC# 002/2006
Investigators: *Kandasamy R, Madouj A, Zahrani A, Hashim S*

Project Description

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

Progress

Population trees were generated in SAS® (batch mode) for each GCC country. These charts were presented in the GCCR Annual/Cumulative Report. Interactive population trees were generated, as well.

Project Title: Pan Arab Liver Transplantation Registry.
RAC Project # 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 vital 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 reports were modified.

Project Title: Thromboembolic Disorders Registry.
RAC Project # 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 Project # 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 Project # 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 Project # 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 Project # 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 Project # 991 029, BESC# 018/1999
Investigators: *Al Shail E, Shoukri M, Yassen I, Subhani S, Al Abdulaaly A, Al Zayed Z, Kattan H, Kurdi W, Sakati N, Hashim S*

Project Description

Neural Tube Defects (NTD) are serious birth defects with symptoms that range from mild to severe degrees. They are a group of birth defects, which have a common origin in failure of the neural tube to develop properly during the embryonic stage. The King Faisal Hospital and Research Centre Neural Tube Defects Registry was established in March 2000 through the joint efforts of the departments of Neurosciences and Biostatistics, Epidemiology and Scientific Computing (BESC), Pediatrics, Orthopedics, Urology, and Obstetrics and Gynecology. The registry is designed for the collection, management and analysis of data belonging to patients with

NTD. The NTD registry is located within the BESC department at King Faisal Specialist Hospital 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.

Progress

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.

Project Title: Saudi National Mental Health Survey.
RAC Project # 209 1 093, BESC# 004/2010

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

Project Description

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

Progress

Discussed project with PI. Read 3 published papers concerning the study and attended 3 SAS analytical courses in preparation for providing statistical analysis for the project in the near future.

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BRU Training

- Summer Training Lectures.
- Research Methodology course.
- Biostatistics Research Methods course.
- Business Mathematics course for Medical Secretaries Program & Auditors Program.
- SPSS training for ERU staff.
- Training graduated students during summer for more than 3 months.
- Provide SAS training
- Provide technical guidance/assistance to staff on SAS related issues
- Participating in an online course in SAS® Enterprise Guide (the point-and-click version of SAS) in order to be able to train SAS end users

Data Clinics

- Several clinical data analysis.
- Consultation on walk-in projects (Data Clinics) for the following departments:
  - Comparative Medicine
  - Biostatistics, Epidemiology, and Scientific Computing
  - Biological and Medical Research
  - Stem Cell Therapy Program
  - Medical and Clinical Operations
  - Department of Medicine
  - Oncology Department
  - Department of Neurosciences

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 specialties. Our mission is dedicated to understanding the patterns and causes of health and disease, and the application of that knowledge in improving the health of populations. The 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), 4 technical and 2 administrative staff.

Scientists within the ERU have strong links to other institutions and programs, serving as advisors, committee members or collaborating co-investigators at the International Epidemiological Association, King Saud University, Ministry of Health, King Abdulaziz Medical City, Prince Salman Center for Disability Research, Harvard University, University of Michigan, 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 annual Research Methodology course has received excellent reviews and will be instrumental in capacity building of future researchers. Recently, ERU scientists have participated in organizing and lecturing in the IEA International Course on Epidemiological Principals and Methods. ERU scientists have also taught university courses at King Saud University and at the King Saud bin Abdulaziz University for Health Sciences. In addition, the unit's staff have supervised several Saudi graduate students, who have benefited from the experience and knowledge of the ERU scientists and their access to ongoing studies.

HEAD OF UNIT

Yasmin Al Twaijri, PhD

STAFF MEMBERS

Abdulaziz Al Othaimeen, PhD
Ali Al Zahrani, MD, PhD
Ravichandran Kandasamy, PhD
Amal Al Madouj
Batlah Al Murshed
Abdulrahman Bin Muammar
Abdullah Al Joudi, PhD *(Adjunct)*
Mansour Al Joufan, MD *(Joint Appointment)*
Saud Al Shanefey, MD *(Joint Appointment)*

RESEARCH PROJECTS

Project Title: Saudi National Mental Health Survey.
RAC Project # 209 1 093)
Principal Investigators: *Yasmin Al-Twaijri, Abdullah Al-Subaie*
Co-Investigators: *Abdulhameed Al-Habeeb, Mohamed Shoukri, Mohammed Al-Sekait, Fahad Al-Wahabi, Abdulaziz Al-Dekhil, Ali Al-Zahrani, Naseem Qureshi*

Project Description

The Saudi National Mental Health Survey is a collaborative project which is administered by the Prince Salman Center for Disability Research (PSCDR) in collaboration with KFSH&RC, Ministry of Health, King Saud University (KSU), King Abdulaziz City for Science and Technology (KACST), Ministry of Economy and Planning, and Harvard University. Funding for the study will be from PSCDR/Abraj Capital, KACST and KSU.

Mental health disorders are a major public health problem worldwide. Besides causing significant impairment to the personal, social and occupational functioning of the individual, there are also significant costs to society in lost worker productivity and utilization of health care resources.

Epidemiological surveys of diseases are important for identifying prevalence & risk factors, elucidating phenomenology and studying prognosis and outcome of treatment. It is also important in providing vision for future planning of relevant preventive, therapeutic, and rehabilitation services in the society.

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

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

Progress

Study proposal has been approved by ORA. Grant funding has been approved by Prince Salman Centre for Disability Research, KACST, and KSU. The CIDI questionnaire has been translated from English to Arabic and reviewed by a team of psychiatrists and psychologists and survey research consultants. Interviewer training sessions for pre-testing of the instrument via cognitive interviewing has been completed.

Project Title: Modeling Familial aggregation of cleft lip/plate: A hospital based registry study.
RAC Project # 2101 004)
Investigators: *Ravichandran Kandasamy, Yasmin Altwaijri, Mohamed Shoukri, Aziza Al-Johar, Shazia Subhani*

Project Description

Several studies showed Cleft lip/palate (CL/P) are known to recur in families and the risk of having a second infant with CL/P after given birth to a first infant with same defect

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

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

Progress

Study proposal has been approved by ORA

Project Title: Riyadh Puberty Study.
RAC Project # 2081 020)
Investigators: Alwan I, Felimban N, Altwaijri Y, Shoukri M, Tamimi W, Almutair A, Tamim H

Project Description

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

Progress

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: Epidemiology of Asthma in Mecca and Medina.
RAC Project # 2081 121)
Investigators: *Syed Hasnain, Mohammad Osman Gad-El-Rab, Yasmin Altwaijri*

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 anemophilius (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: Knowledge, Awareness and Attitude About Cancer and Its Prevention.
RAC Project # 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

Detailed analysis showed poor understanding of the risk factors, screening/early detection methods and misconceptions about treatment of cancer among nationals. Further, this survey provided baseline information on community level knowledge, attitude, and preventive practices about cancer and also provided information for educators and policy makers that are necessary for guidance towards better cancer awareness programme in this region. Final report of the project was submitted to KACST. The final report to RAC was accepted. One presentation entitled, 'A study on knowledge and awareness about cancer and its prevention, Riyadh, Saudi Arabia' was accepted in the 5th Asian Pacific Organization for Cancer Prevention. A manuscript entitled, 'Public knowledge on cancer and its determinants among Saudi population' was submitted to BMC cancer.

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

During the ten-year period (1999-2008) this registry registered a total of 1187 cases with a male to female ratio of 1.3: 1. There were 1135 Saudi (M=640; F=495) and 52 Non-Saudi (M=23; F=29) cases registered over the ten year. Most of the cases (1172; 98.7%) were from Saudi Arabia. Riyadh region had more number of cases (364; 31.1%) followed by Eastern (169; 14.4%) and Asir (167; 14.2%) regions. A total of 86 (M=50; F=36) cases were born and registered from KFSH&RC and the remaining 1101 (M=613; F=488) cases were referred to KFSH&RC from other hospitals. About 53% of the cases parents were of first cousin and more than one quarter of the cases (28.0%) have a family history of deformities. Siblings of the patient had a history of deformities more than any other relations among first cousin.

Out of the 1187 cases 774 (65.2%) cases had only cleft of lip and/or palate, 132 (11.1%) cases had only craniofacial anomalies and 281 (23.7%) cases had both CLP and CFA. There were 592 males and 463 females with CLP; the male to female ratio is 1.3:1. Overall, unilateral cleft lip and palate was common (248; 23.5%) closely followed by bilateral cleft lip and palate (243; 23.0%). However, cleft of hard palate was common in female, and in male the cleft lip and palate was more common with equal number in bilateral and unilateral CLP. There were 224 male and 189 female cases of craniofacial anomalies with a male to female ratio of 1.2:1. Out of the 413 craniofacial anomalies, 245(59.3%) cases had only facial, 100(24.2%) had only cranial and 68(16.5%) had both the anomalies.

Out of the 12,189 total procedures done so far the primary surgeries like Initial lip & nose repair, Initial palate repair accounts to 5.3% and 5.9%, respectively. Also, P.E. Tube placement and speech therapy accounts to 6.5% and 12.7%, respectively, of the total procedures. About 83% of primary surgeries (Initial lip & nose repair, Initial palate repair) were done at KFSH&RC and the rest were done outside KFSH&RC. Out of the 644 initial lip & nose repair,

510 (79.2%) were done in KFSH&RC and out of 719 initial palate repair, 617 (85.8%) are done in KFSH&RC.

A report, 'Cleft Lip/Palate and Craniofacial Anomalies Registry: Cumulative Report 1999-2008' was published. An article describing the incidence of craniofacial anomalies was submitted to a peer reviewed journal.

Project Title: Impact of Tube Feeding on Aspiration Pneumonia.
(RAC Project # 2091 061)
Investigators: *Muneera Al-Bugami, Yasmin Altwaijri*

Project Description

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

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

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

Tube feeding is a recognized method for nutritional support in patients known to have difficulty in swallowing due to: dementia, brain stroke and others. The tube is placed percutaneously through a stoma created on the abdomen (gastrostomy or jejunostomy), using endoscopic or radiological techniques.

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

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

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

Progress

Study proposal has been recently approved by ORA.

Project Title: Metabolic Syndrome Prevalence Among Childhood Acute Lymphoblastic Leukemia (ALL) Patients After the End of Treatment.
RAC Project # 209 1 043
Investigators: *Abdallah Al-Nasser, Yasmin Altwaijri, Fahad Al-Dhafiri, Hanan Al-Mutairi*

Project Description

The metabolic syndrome (MS) is " a grouping of clinical characteristics including insulin and insulin resistance (IR), abdominal obesity, impaired glucose tolerance, elevated blood pressure (BP), elevated triglycerides (TG) and reduced high-density lipoprotein cholesterol (HDL-C)'[1].

MS in childhood and adolescence is a growing concern. The prevalence of MS is variable and is dependent on the diagnostic criteria and population, but it is increasing in children and adolescents [2], and the availability of recently agreed International Diabetes Federation (IDF) definitions of MS in a more standardized and acceptable way.

All is the most common childhood malignancy, and prevalence of obesity and other features of the MS are probably common both during and after therapy for ALL [4]. Mertens et al. reported an increased risk of all-cause mortality, cardiovascular-related mortality, cerebrovascular accidents, and chronic health conditions in long-term survivors of childhood All [5]. However, our literatures search conducted earlier in 2009 has found no large studies of prevalence of MS in survivors of All (no studies with n>50), and no studies which used recent IDF criteria to define MS, and so a study of the prevalence of MS in survivors is necessary.

Progress

Study proposal has been approved by ORA; data was collected and is now being analyzed.

Project Title: Spatial-Temporal Analysis of Breast Cancer Incidence in Saudi Arabia.
RAC Project # 2101 008
Investigators: *Ravichandran Kandasamy, Mohamed Shoukri, Yasmin Altwaijri, Shouki Bazarbashi, Haya Al-Eid, Shazia Subhani*

Project Description

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

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

Progress

Study proposal has been approved by ORA

Project Title: Modeling Familial Aggregation of Cleft Lip/Plate: A hospital Based Registry Study.
RAC Project # 2101 004
Investigators: *Ravichandran Kandasamy, Yasmin Altwaijri, Mohamed Shoukri, Aziza Al-Johar, Shazia Subhani*

Project Description

Several studies showed Cleft lip/palate (CL/P) are known to recur in families and the risk of having a second infant with CL/P after given birth to a first infant with same

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

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

Progress

Study proposal has been approved by ORA. Data acquisition is in process.

Project Title: Spatial-Temporal Analysis of Breast Cancer Incidence in Saudi Arabia.

RAC Project # 2101 008

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

Project Description

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

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

Progress

Study proposal has been approved by ORA.

Registries Core Facility

Established in year 2000 this core facility in the Department of Biostatistics, Epidemiology and Scientific Computing is charged with the responsibility of setting up, maintaining, and development of hospital-based as well as regional and population-based disease registries.

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 administrative and research projects. Throughout the year 2009 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. 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.

HEAD OF FACILITY

Shazia Subhani, MSc

STAFF MEMBERS

Nadia Dessouky, MD
Ahsan Yaseen, MPH
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Ehsan El-Shamy BSN
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Lina Barhoush, BS *(Grant)*
Mona Hagos, BSc *(Grant)*
Hala Al Assiry, BA *(Grant)*
Nada Bawyan *(Grant)*
Saleh Abdulkadir Saeed *(Grant)*

RESEARCH PROJECTS

Project Title: Congenital Heart Defects Registry (CHDR).
RAC Project # 99 1026
Investigators: *Zohair Halees MD, Mansour Al Jufan MD, Futwan Al Mohanna PhD, Mohamad Shoukri PhD, Ahmad Omrani MD, Shazia Naz Subhani MSc, Nadia Dessouky M*

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, Dammam Maternity & Children Hospital, King Fahad Medical City, Riyadh in terms of remote data acquisition and patient data registration.

Progress

- Data audited prior to cumulative report tabulation.
- Cumulative report for (1998 – 2008) submitted.
- Progressive Collaborations
- Meetings and user trainings for King Fahad Medical City, Riyadh and Maternity and Children Hospital, Dammam.

Presentations

- N. Dessouky, "Registry Features and Concepts: Saudi Congenital Heart Defects Program". Saudi Heart Institute Annual Meeting 2009.
- Joufan M, Management of Congenital Heart Disease in Saudi Arabia. American College of Cardiology Annual Meeting, 28-31 March 2009, Orlando, USA.
- Statistics for all year cases as of December 31, 2009 is listed in Table 1.
- Statistics for year 2009 is listed in Table 2.
- New version of the CHD registry application launched along with the new website. http://rc.kfshrc.edu.sa/chd_program.
- An E-Forum (Blog) designed and launched for the committee members.
- Data released from the CHD registry for Research Proposal entitled "Fetal Cardiac Screening, How to improve the Detection of Prenatal Screening for Congenital Heart Defects".

Publications

- Multi-Institutional Cumulative Report (1998 – 2008)
- N. Dessouky, Poster Abstract "Registry Features and Concepts: Saudi Congenital Heart Defects Program". 7th Gulf Heart Association Meeting, 9-11 April 2009, Dubai, UAE.

Table 1

Collaborating Hospitals	New cases	Follow up cases	Diagnosis coding	Treatment coding
(KFSH&RC, PSSC, Dammam Maternity & Children Hospital)	17707	42094	17707	18213

Table 2

Collaborating Hospitals	New cases	Follow up cases	Diagnosis coding	Treatment coding
(KFSH&RC, PSSC, Dammam Maternity & Children Hospital)	1386	1189	1025	816

Project Title: Neural Tube Defects Registry (NTDR).
RAC Project # 99 1029E
Investigators: *Essam Al Shail MD, Mohammad Al Abdulaaly MD, Zayed Al Zayed MD, Mohamad Shoukri PhD, Hoda Kattan MD, Wesam Kurdi MD, Nadia Sakati MD, Shazia Naz Subhani MSc, Ihsan Yassen MPH*

Project Description

Neural Tube Defects refer to a group of lesions that occur at various positions along the spinal cord, which are ultimately due to a defect in the closure of the neural groove to form an intact neural tube. Anencephaly, spina bifida and encephalocele account for almost all NTD's. The King Faisal Specialist Hospital and Research Centre established in March 2000 a registry for all patients with neural tube defects presenting to the hospital. The registry is a coordinated collaboration among the departments of Neurosciences, BESC, Pediatrics, Orthopedics, urology, and Obstetrics and Gynecology. The purpose of the registry is collection, management, and analysis of data belonging to patients diagnosed with NTD and presenting to KFSH&RC.

Active data acquisition and registration is on-going from KFSH&RC and the collaborating hospitals; Disable Children Hospital, Maternity & Children Hospital, Dammam and Riyadh Medical Complex, Riyadh.

Progress

- Data audited prior to annual report data tabulation.
- Registry staff participated in 2 Spina Bifida Awareness Days events. One in National Guard and the other in King Faisal Specialist hospital & Research Centre.
- On-going collaboration with regional hospitals
- Statistics for all year as of December 31, 2009 is:

	New cases	Follow up cases
Collaborating Hospitals	605	278

- Statistics for year 2009 is:

	New cases	Follow up cases
Collaborating Hospitals	44	44

Future Directions

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

Publications

Seventh Annual Report with Registrations from October 01, 2000 till December 31, 2008.

Project Title: Epilepsy Registry.
RAC Project #: 2011-059
Investigators: *Abdulaziz Al Semari MD, Aziza Chedrawi MD, Hisham Al Dhalaan MD, Ibrahim Thubaiti MD, Salah Baz MD, Suad Al Yamani MD, Shazia Naz Subhani MSc, Najah Aftab Siddiqui MSc*

Project Description

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

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

Progress

- Data audited prior to cumulative report data tabulation.

- Registry Data Presentations as follows:
  - National Epilepsy Program Update, 17th Annual Neurosciences Symposium, Medina - Feb 2009
  - Parietal Occipital Lobe Epilepsy, Management of Intractable Epilepsy Symposium, King Faisal University, Dammam - June 2009
  - "Epilepsy and elderly people" S. Baz, A.AlSemary, I. Althubaiti. 17th Annual Saudi Neurosciences Symposium. Medina - February 2009
  - Temporal Cases Presentation at King Faisal University, Dammam - June 2009
  - "Demographics and characteristics of patients with Generalized Epileptogenic potentials from a tertiary care setting in Saudi Arabia" 28th International Epilepsy Congress. Budapest - October 2009
  - "A look at our experience in subdural recording for refractory epilepsy patients" 28th International Epilepsy Congress. Budapest - October 2009
  - Neurophysiology Data in poster presentation during Quality Day 2009. KFSHRC
- Statistics for all year as of December 31, 2009 is:

	New cases	Diagnosis	Surgery
Collaborating Hospitals	3562	2544	455

- Statistics for year 2009 is:

	New cases	Diagnosis	Surgery
Collaborating Hospitals	381	475	96

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

- Multi-institutional Annual Epilepsy Registry Report (2008)

Project Title: Cleft Lip / Palate and Craniofacial Anomalies Registry (CLCPR).
RAC Project # 991-030
Investigators: *Aziza Al Johar MD, Essam Al-Shail MD, Abdulaziz Al Rubaiya MD, Kandasamy Ravichandran PhD, Shazia Naz Subhani MSc, Ebthisam Al Jarba BA*

Project Description

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

Progress

- Cumulative report (1999–2008) published after data validation and auditing.
- Several national presentations on registry data as follows:
  - CLCP Registry Functionalities: 2nd International Cleft Lip and Palate workshop. 31 March–02 April 2009, KFSHRC
  - Epidemiology of Cleft in Saudi Arabia: 2nd International Cleft Lip and Palate workshop. 31 March–02 April 2009, KFSHRC
- Statistics for all year as of December 31, 2009 is:

	New cases	Diagnosis coding	Treatment coding
King Faisal Specialist Hospital & RC	1317	1341	4099

- Statistics for year 2009 is:

	New cases	Diagnosis coding	Treatment coding
King Faisal Specialist Hospital & RC	132	130	480

Publications

- Cumulative Cleft Lip/Palate and Craniofacial Anomalies Registry Report (1999 - 2008).

Project Title: Thromboembolic Disorders Registry (TEDR).
RAC Project # 2001045
Investigators: *Abdulaziz Al Harthi MD, Jalal Saour MD, Habib Bassil MD, Layla Mammo MD, Mohamad Shoukri PhD, Mansour Aba Al Khail MD, Mustafa El Naggar MD, Mona. El Sherif MD, Shazia Naz Subhani MSc, Ehsan El-Shamy BSN*

Project Description

Thromboembolic disorders are important causes of mortality and common causes of morbidity in the Kingdom of Saudi Arabia. The true incidence of these disorders in the Kingdom is not known but it is unlikely to be less than that reported in the Western countries. TED Registry is to serve as a repository of data specifically for patients with Thromboembolic disorders. This will enable contributors to the registry to analyze outcomes of management, to optimize treatment and improve outcomes. All patients referred to the Thromboembolic Service for anticoagulation therapy at KHSH&RC are included in the registry.

The Thromboembolic Disorders (TED) Registry of King Faisal Specialist Hospital and Research Centre were established in February 2001 as collaboration between Biostatistics, Epidemiology and Scientific Computing (BESC) Department and Internal Medicine Department. All patients presenting to the Thromboembolic Service in the section of Internal Medicine are registered after getting their informed consent.

Progress

- Data audited prior to cumulative report data tabulation.
- Grand round presentations
- Statistics for all year as of December 31, 2009 is:

	New cases	Follow up cases
King Faisal Specialist Hospital & RC	2915	3684

- Statistics for year 2009 is:

	New cases	Follow up cases
King Faisal Specialist Hospital & RC	247	127

Publications

- Thromboembolic Disorders Registry Cumulative Report (2001 - 2008).

Project Title: Venous Thrombosis and Thrombophelia Disorders Registry (VTFT).
RAC Project # 2001 017
Investigators: *Jalal Saour MD, Layla Mammo, Mohamad Shoukri PhD, Shazia Naz Subhani MSc, Ehsan El-Shamy BSN*

Project Description

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

Progress

- Abstract Presentations: J Saour, M Shokri, L Mammo. The Saudi Thrombosis and Familial Thrombophilia-

Results of five factors tested. 21st Congress of Thrombosis and Heamostosis, Boston, USA, July 2009.
- Collaboration invitations to major hospitals in KSA
- As of December 31, 2009 total counts in the database is: 1227 cases
- For year 2009 patients registered are: 143 cases

Future Directions

- National collaborations

Project Title: Neuromuscular Disease Registry (NMDR).
RAC Project # 99 1029E
Investigators: *Mohammed Al Muhaizea MD, Saeed Bohlega MD, Bent Stigsby MD, Hisham Al-Dhalan MD, Shazia Naz Subhani MSc, Ahsan Yassen MPH*

Project Description

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

Progress

- NMDR data was requested for a spin-off research study on Limb Girdle Muscular Dystrophy called “The Pathology and Genetics of Limb Girdle Muscular Dystrophy in Saudi Arabia”.
- 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, 2009 is:

	New cases	Diagnosis coding	Treatment cases
King Faisal Specialist Hospital & RC	2074	2074	2564

- Statistics for year 2009 is:

	New cases	Diagnosis coding	Treatment cases
King Faisal Specialist Hospital & RC	397	397	384

Publications

- Neuromuscular Disease Registry 2008 Annual Report.

Project Title: National Diabetes Registry (Research Centre administration approved).
Investigators: *Khalid Rubean MD, Mohamad Shoukri PhD, Shazia Naz Subhani MSc*

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 27 hospitals) from all over Riyadh region.

Progress

Presentations:

- S.Subhani, "Use of GIS within Web-Based Saudi National Diabetes Registry", 2009 ESRI Health GIS Conference, September 2009, Nashville, Tennessee, USA.
- S. Subhani, "Health data projection using GIS", 2009 ESRI Middle East and North Africa User Conference (MEAUC), November 2009, Manama, Bahrain.
- Lectures given in the "Diabetes Educators Courses"

Future Directions

- Collaboration expansion on National Level

Publications

- S.Subhani, "Use of Geographical Information System in the Web-Based Saudi National Diabetes Registry", 2009 *International Journal of Geo-Informatics* (IJG) Vol.5, No.1.

Project Title: National Family Safety Registry (NFSR).
RAC Project # 2081 050
Investigators: *Huda Kattan MD, Maha Muneef MD, Majid Al Eissa MD, Shazia Naz Subhani MSc*

Project Description

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

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

Progress

- National Family Safety Registry By Laws completion.
- Successful implementation of the web-based registry application.
- User trainings at KFSH&RC (2 days) for all centers with 26 participants.
- Total of 132 cases registered in the centralized database as of December 31, 2009.

Future Directions

- Visits to Family Safety Centers on National Level for comprehensive user trainings

Project Title: Pan Arab Liver Transplantation Registry (PALTR).
RAC Project # 2071 022
Investigators: *Professor Mohamed Al-Sebayel MD, Hatem Khalaf MD, Khalil Alawi MBBS, Mohamad Shoukri PhD, Shazia Naz Subhani MSc*

Project Description

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

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

Progress

- Establishment of new collaboration with Cairo University, Egypt.
- On-going collaboration with Wade-e-Nyle, Egypt.
- As of December 31, 2009 a total of 560 patients registered in the centralized database.
- On-going data collection and entry in the registry database.

Future Directions

- Pan Arab Level Collaborations

Project Title: Rare Dental Disorders Registry (RDDR).
RAC Project # 2071 082
Investigators: *Adeeb Al Omrani BDS, DMSc, Hans Hansson DDS, Richard Hakansson DDS, PhD, Khalid Al Zoman BDS, MS, Shazia Naz Subhani MSc*

Project Description

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

Progress

- Registry web application design in progress.
- Data capturing on the case report forms for later registration in the database.

Future Directions

- Collaborations

Project Title: Primary Immunodeficiency Registry (PIDR).
RAC Project # 2081 111
Investigators: *Bandar Al Saud MD, Saleh Al Muhsen MD, Abdulaziz Al-Ghonaium MD, Hmoud Al-Musa MD, Hasan Al-Dhekry MD, Sulaiman Al-Gazlan MD, Hasan Al-Rayes MD, Rand Arnaout MD, Nazeema Elsayed, Mohamad Shoukri PhD, Shazia Naz Subhani MSc*

Project Description

Primary Immunodeficiency Diseases reflects abnormalities in the development and maturation of cells of the immune system. These defects result in an increased susceptibility to recurrent infections. Although they all share such finding, they are very heterogeneous group of disorders in their clinical presentations and underlying pathophysiology. To address this problem the department of paediatric in collaboration with Registries Core Facility at BESC department, Research centre developed a registry proposal which was approved by Research Advisory Council in the year 2009. The aim of the registry is for a long term documentation of patient. The rationale for developing this registry is to determine the magnitude of disease and types of PID disease encountered in our population at KFSH&RC. Upon successful data collection other health care centres in Riyadh and subsequently cross the country will be added, to have national representation of the registry.

Progress

- Case Report Forms designed.
- Identification of man power for the registry.
- Web-based application design in progress.

Future Directions

National collaborations.

Computing Services Core Facility

MISSION

To provide and maintain up-to-date computing facilities for use in scientific research.

The Computing Services Core Facility is playing a major role by providing information technology support to the Research Centre which is a research 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 FACILITY

Parvez A. Siddiqui

STAFF MEMBERS

Mashnouf Al Rowaily
Arnie S. Tayco
Yousef Hussain
Michael Edquiban *(Grant)*
Bandar Al Khodairy *(Scholarship Leave)*

TRAINING COURSES

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

Training and Seminars

- Innovative Approach in Radiotherapy March 9-12, 2009
- PACS Administrator Course on: PACS Technology Review, Acquisition, Implementation and Clinical Operation, April 6-8, 2009
- Biostatics Research Methods, April 25-27, 2009
- The Biological Weapons Convention Awareness, October 20-21, 2009
- Scholarship - Mr. Bander AlKhodairy

Courses Attended by CSCF Staff members

- Operation Management, Personal Effectiveness (*Arine Tayco*)
- Decision Making, Managing in Tough Times, Managing in Tough Times, (*Mashnouf Al-Rowaily*)
- Biostatics Research Methods (*Michael Edquiban*)

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 2009, CSCF setup new PCs, laptops, workstation, printers, servers and other major computer peripherals. The CSCF was successful in restoring and reconfiguring IBNKHALDUN server after hard disks failure. CSCF was successful setup and configured IBNHAIYAN server for hosting Genetics data.

CSCF replaced TDBCF staff laptops with Desktops to satisfy their needs for more computers power which going to promote their productivity.

CSCF setup and configured:

- 76 new PCs and distributed to assigned departments.
- 15 new laptops
- 12 new black and white printers.
- 7 new color printers
- 6 new scanners

Preventative Maintenance

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

These tasks are related but not limited to:

- Operating systems update
- Disk defragmentation,
- Software updates
- Service packs for windows and MS Office
- Cleaning internet browser temporary internet and offline files
- Updates of the anti-virus software

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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 departments.

Pre-procurement Analyses

Work involved in determining system configuration for new computers, be these user PCs, instrument PCs, or

additional servers, is a CSCF concern. Further, CSCF makes sourcing recommendations that cover vendor comparisons, price-performance analyses, and post-sale support assessments.

KFNCCC&R Support

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

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

ITA and CSCF

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

Core Facility activities breakdown by department

CSCF setup and configured PCs, Laptops, Workstations, Printers, and Scanners for the following departments:

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

Following is the summary of the calls per department logged by CSCF during the year 2009

Department	No. of Logged Calls
BESC	627
BMP	340
BMR	392
CCR	157
CMD	155
CPPEO	147
C&R	159
Genetics	540
ORA	187
RC-Admin	323
Stem Cell Therapy	165
T&E	94
KFNCCC-Research (CDU)	102
KFNCCC-Research (SDL)	97
KFNCCC-Research (HCGL)	100

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 FACILITY

Saleh Al Ageel

STAFF MEMBERS

Bushra Siddiqui, MSc
May Al Husseini, MSc
Lyna Al Fantoukh
Hibah Azem
Fahad Al Enazi
Mansoor Baig *(since August 2009)*

CORE FACILITY ACTIVITIES

Applications (developed/being-developed year 2009)

Design and Development web based application for National Family Safety Registry.

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

Design and Develop web based application for Saudi Arabia Pediatric Hematology Oncology Society (SAPHOS)

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

Design and Develop database for Bio-Tech Project Management System for Science & Technology.

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

Design and Develop database for Financial Management and Accounting System (TDBCF involvement 30%).

Financial Management and Accounting System is a centralized web-based application specially designed to suit the needs of Research Centre Administration's financial transactions. The web application allows only authorized users to access the system thereby allowing them to collect, process, maintain, transmit and report data about financial events.)

Radiation Medicine

Designed and developed a website for biomedical physics (*http://www.radmed.org*) for the international conference on radiation medicine for the international seminar at KFSH&RC.

This site will be used for the current as well as future conferences.

Medical Second Opinion System

The Medical Second Opinion is a web-based application designed for the Health Outreach Office to serve as a work flow for the Medical Second Opinion form. The application enables users to self-register themselves. After approval of the registration, the users can fill out the electronic form and submit it for review by the coordinator, manager, and executive director of the Health Outreach Office.

Moreover, the application enables the users to search, generate reports, and produce lists related to the electronic form

Applications re-developed (New Versions)

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

TDBCF has planned to provide a technology upgrade to the older projects and convert and port these applications on a ASP.NET or Enhance the applications to include more dynamic capabilities using AJAX.

This upgrade will improve the application security, reliability, performance.

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 2009)

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

Application for Oligonucoletide 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.

Middle East Childhood Cancer Alliance (MECCA)

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

Ongoing Application (Users Support & Maintenance)

Breast Cancer Samples Management Application

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

Arabian Horses Web Application

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

Neuropsychology Database

Neuropsychology Database is a web-based application

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

Billing Data Management System

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

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

CV Database

CV database is a web-based application developed for Research Centre Administration to keep applicants *Curriculum Vitae* available electronically to authorized personnel of the organization. The application was developed with the intent to facilitate people who want to hire people with specific qualifications/experience. Besides entry of applicants' qualifications/experience, the application provides extensive search screen to search the candidate of one's choice.

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.

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.

Thermo Luminiscent Dosimetry (TLD)

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

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

National Laboratory for NewBorn Screening

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

Saudi Thrombosis and Familial Thrombophelia Registry

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

Thromboembolic Disorders Registry

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

Cyclotron Maintenance Database

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

Neuromuscular Diseases Registry

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

Research Centre Grant Leave Database

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

Users' Training

- TDBCF Section is committed to provide users training sessions at the completion of each application.
- TDBCF has provided several training sessions for users of the National Family Safety Registry user's.

Professional Training

TDBCF Trainees

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

The Trainee is made a part of a current ongoing project where he/she passes though the real project development cycle so

as to get a feel of actual software design and development which is not limited to just the theoretical understanding.

A new TDBCF staff member, who joined during the year 2009, has successfully completed the training which was impacted by the team members of TDBCF.

TDBCF DEMO's

A demonstration of National I Family Safety Registry Web application has been done. That was developed with the collaboration of National Family Safety Program during the opening ceremony of the registry.

The Department of

BIOMEDICAL PHYSICS

Biomedical Physics

The Biomedical Physics Department has continued to fulfill its goals and objectives to ensure better services in response to increasing demand for provision of quality health care, consultation, continuing education and research in line with internationally acceptable standards.

The Biomedical Physics Department held its 1st Strategic Planning Retreat in October 2009. The initiative is envisioned to build a stronger and more vital Department that brings more rigor to the process of setting goals and to strategically focus its resources. It was also an opportunity to discuss issues critical to the long-term direction of the Department and to develop an updated strategic plan with emphasis on creating action plans to guide the program activities of the department in the next few years. We envision a future that includes departmental growth and development matched by acquisition and implementation of current innovations and competent staff in support of the KFSH&RC mission of maintaining the status of being the diamond of healthcare.

CHAIRMAN

Belal Moftah, PhD, FCCPM

ADMINISTRATIVE STAFF

Al-Assalain, Dena
Banguilan, Irene, BSc *(RC Grant)*
Co, Marilou, BSc *(RC Grant)*
San Pedro, Mildred, BSc *(RC Grant)*
Venturina, Lorcel Aubrey, BSc *(RC Grant)*
Venturina, Lorcel Ericka, BSc *(RC Grant)*
Veridiano, Josephine, BSc

DEPARTMENT ACHIEVEMENTS

In spite of staffing shortage, the Department managed to have the following major achievements in 2009:

- Historic event for the introduction of four major radiotherapy treatment modalities (TomoTherapy, CyberKnife, RapidArc and Large Bore CT) into clinical practice at KFSH&RC. This makes KFSH&RC the first and only institution in the whole world to have these modalities, and the first to have any one of these modalities in the region. In collaboration with Radiation Oncology and Radiation Therapy of the Oncology Centre, first patients were successfully treated using all these modalities in May and July 2009.
- Increase in the number of patients and tumor sites treated with the advanced mode of high-precision Intensity Modulated Radiation Therapy making IMRT a routine cancer treatment technique at KFSH&RC.
- Continued recognition of the department expertise by the International Atomic Energy Agency (IAEA). Selection of a member of the department to be one of five eminent experts to provide comprehensive professional assessments and advice on all current IAEA projects (373) in the area of nuclear applications of human health, at the request of the IAEA Director General. Also, the department coordinated the IAEA Expert Mission visit for the establishment of a Proton Carbon Ion Therapy Centre. Mission included six distinguished Experts (Professors Jean Bourhis, Hirohito Tsuji, Koji Noda, Jacob Flanz, E.H. Zubizerreta, Jake van Dyk).
- Hosting of the international conference on “Innovative Approaches in Radiotherapy: Beyond Tomorrow” and the IAEA Regional Training Course on Quality Assurance for Treatment Planning Systems”, in cooperation with King Abdulaziz City for Science and Technology and the International Atomic Energy Agency.
- Establishment of a Molecular and Functional Imaging Group.
- Development of staff expertise through internationally recognized board certifications: Dr. Belal Moftah became a Fellow of the Canadian College of Medical Physicists in Medicine; Dr Omer Demirkaya became a diplomat of the American Board of Science in Nuclear Medicine.
- Completion of scholarship study by two staff members of the Department: one PhD (Dr Huda Al-Mohammed) and one M.Sc. (Mrs Hind Al-Selham).
- Securing of practice licenses for the various departments and radiation practices within the hospital such as Nuclear Medicine, Radiation Therapy, Research, and radiopharmaceuticals production. Some of these licenses had been bending for years.
- Thermoluminescent Dosimetry (TLD) radiation monitoring services offered to about 100 institutions using our IAEA and WHO accredited TLD Laboratory.
- Calibration of 1,161 radiation survey devices of about 100 institutions nationwide by our IAEA accredited Secondary Standard Dosimetry Laboratory. The workload represents 83% increase from the previous year.
- Publication of the first worldwide scientific demonstration of a link between radiosensitivity and mitochondrial DNA genetic variations in cancer patients.
- Publication of 5 manuscripts in specialized scientific international journals in addition to public media news.
- Department participation in major KFSH&RC projects: (1) Proton-Carbon Ion Therapy Proposal, King Abdullah Center for Oncology and Liver Disease; (2) Cooperation Agreement between KACST and KFSH&RC; (3) International Atomic Energy Agency Project No. SAU2008001 “Establishment of King Abdullah Oncology Centre”; (4) International Atomic Energy Agency Project No. RAS2007030 “Clinical Residency Training Program in Medical Physics

RESEARCH PROJECTS

The research activities of the Department in 2009 resulted in a number of publications in specialized international scientific journals. Details are shown in the sections’ reports.

FUTURE RESEARCH DIRECTION

The Biomedical Physics Department will continue to focus on cutting-edge research aimed at improving the quality of patient care in our institution. The future research direction for each section of the department is shown in the sectional reports.

PUBLICATIONS

We have a considerable number of publications in 2009, which are detailed in the respective Department sections’ reports.

The 2009 annual reports of the following sections and core facilities of the Department are shown in separate reports:

BIOMEDICAL PHYSICS DEPARTMENT	
Sections	**Core Facilities/Unit**
1. Radiation Physics	1. Radiation Safety Office
2. Imaging Physics	2. Gamma Irradiation Facility
3. Health Physics	3. Secondard Standard Dosimetry Laboratory
4. Biomedical Physics Research	4. Clinical Dosimetry and Treatment Planning Unit
5. Molecular and Functional Imaging	

Biomedical Physics Research (Radiation Biology)

The Radiation Biology section continued its close collaboration with the Oncology Department. Radiotherapy is a major arm of cancer treatment that is applied to about 50% of the patients. Although ionizing radiation kills tumor cells, it also damage normal tissues giving rise to radiation complications. In a minority of patients these reactions can be severe that compromise the quality of life of cancer survivors. Variations between patients were associated with rare genetic mutations and polymorphic variations in genes localized in the nucleus. Cells however, contain genetic materials that are localized in the mitochondria (mtDNA), the energy producing cytoplasmic organelles. Here we show that mtDNA genetic variations differ between radiosensitive and normally sensitive Head and Neck cancer patients. Radiosensitive patients who developed moderate to severe fibrosis following radiation therapy harbor significantly higher number of variations than patients with little or no radiotoxicity. Therefore, mitochondria contribute to radiosensitivity. Consequently, predictive testing to avoid radiotherapy complications should also take into considerations variation in mitochondrial DNA.

HEAD OF SECTION

Ghazi Alsbeih, MD, PhD

STAFF MEMBERS

Najla Al-Harbi, BSc
Muneera Al-Buhairi, BSc
Khaled Al-Hadyan, BSc
Sarah Al-Qahtani, BSc *(RC Grant)*
Lorcel Aubrey Venturina, BSc *(RC Grant)*

RESEARCH PROJECTS

Project Title: Investigation of the Role of Mitochondrial DNA Variations in the Expression of Late Normal Tissue Complications Following Radiotherapy.

RAC Project # 2040 025

Investigators: *G. Alsbeih, PhD, K. Abu-Amero, PhD, M. Al-Shabanah, MD, M. Al-Sebaie, MD*

Project Description

The ongoing effort devoted to predictive assays has established the principle that normal tissue complications following radiotherapy are associated with the *in vitro* radiosensitivity of skin fibroblasts. However, the molecular bases of the variations in radiosensitivity between patients remain unclear. Evidence is pointing out a certain number of genetic factors that are involved in DNA repair, cell cycle and the cellular stress response. Ionizing radiations are also known to induce premature differentiation, and accelerated cell aging leading to loss of division potential. These were associated with mitochondrial dysfunction, resulting presumably from accumulating mutations in mithochondrial DNA, which lacks full mechanisms of DNA repair. The impaired function is the result of mtDNA damage inflected by the vicinity of high levels of reactive oxygen species (ROS) issued from ATP energy conversion. The presence of high levels of somatic mtDNA mutations accelerates the process. Radiations are expected to aggravate this situation by damaging the mtDNA itself and increasing the levels of ROS, and consequently lead to cell depletion and the expression of radiation-induced complications. Therefore, we hypothesize that the variation in normal tissue radiosensitivity is the result of a pre-existing high levels of mtDNA mutations and/or polymorphisms. We propose to test this hypothesis in fibroblasts cell strains established from radiotherapy patients with well-documented late normal tissue complications. They are divided into two groups, control and hypersensitive. Full mtDNA will be sequenced following standard procedures. Pathogenicity of novel mutations/polymorphisms is checked and tested by a functional assay for mitochondrial respiratory function. The levels of mutations and/or polymorphisms are compared between the two groups to check for any differences that could correlate with late normal tissue complications following radiotherapy.

Progress

In this progress report we studied the Involvement of mtDNA sequence variations and respiratory activities in late reactions following radiotherapy of Saudi cancer patients.

Purpose: Mitochondria (Mt) and ionizing radiation overlap in a number of features such as both generate harmful reactive oxygen species and that radiation can induce cell death through the intermediary of mitochondria. Since a number of genetic variations in nuclear genes were frequently associated with response to cancer treatment, the aim of this case-control study was to test the hypothesis that mtDNA genetic variations can contribute to patient-to-patient variability in normal tissue response to radiotherapy.

Design: Thirty-two nasopharyngeal carcinomas patients treated with definitive radiotherapy were included. The grade (G) of subcutaneous and deep tissue fibrosis was scored according to the RTOG/EORTC grading system. Coding and RNAs mtDNA (between 611 and 15,978 bp) were sequenced (Figure 1) and genetic variations were scored. Mitochondrial respiratory activity was measured by resazurin reduction assay.

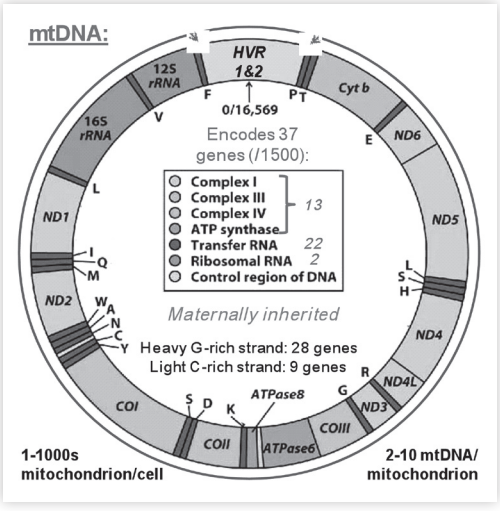


Figure 1: Schematic representation of mitochondrial DNA including encoded genes and the area sequenced in this project.

Results: Data showed significantly (*P* = 0.003) higher number of non-synonymous genetic variations in the radiosensitive (G2-3, 16 patients) as compared to the control (G0-1; 16 patients) groups (Table 1). The non-synonymous A10398G variation in *ND3* gene was significantly associated with fibrotic reaction (P = 0.01). The radiosensitive patients had 7-fold (CI: 1.16-51.65) higher risk of developing moderate to severe fibrosis (G2-3) following radiotherapy (Table 2). This was significantly correlated with lower mitochondrial respiratory activity (*P*=0.001) (Figure 2).

Table 1: Comparison of number of mtDNA sequence variants in the control (G0-1 fibrosis) and the radiosensitive (G2-3) groups of radiotherapy patients.

Patients' group	Total variants (Mean ± SD)	Coding variants (Mean ± SD)	Synonymous variants (Mean ± SD)	Nonsynonymous variants (Mean ± SD)	RNA variants (Mean ± SD)
Control G_0-G_1	288 (18.0 ± 6.6)	194 (12.1 ± 5.0)	168 (10.5 ± 4.5)	27 1.7 ± 1.4)	93 (5.8 ± 2.1)
Sensitive G_2-G_3	334 (20.9 ± 8.0)	241 (15.1 ± 6.4)	188 (11.8 ± 5.5)	53 3.3 ± 1.5)	93 (5.8 ± 2.2)
P value (*t*-test)	0.27	0.16	0.48	0.003	1.00

Table 2: Association study between 3 potentially different mtDNA sequence variants and late normal tissues' complications to radiotherapy.

Gene	Nucleotide	AA change	G_0-G_1		G_2-G_3		Odds ratio (95% CI)	*P*
			W-T	Variant	W-T	Variant		
ND3	10398 A>G	T114A	13	3	6	10	7.22 (1.16-51.65)	0.01
COIII	9540 T>C	Syn	13	3	8	8	4.33 (0.71-29.46)	0.06
ATP6	8701 A>G	T59A	14	2	9	7	5.44 (0.74-49.34)	0.11*

Abbreviations: AA, amino acid; W-T, wild-type; 95% CI, 95% confidence interval; Syn, synonymous.
*Two-tailed Fisher's exact test.

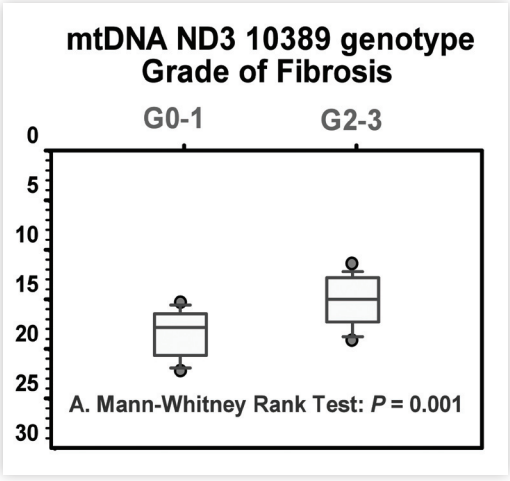


Figure 2: The relationship between mitochondrial respiratory activity (MRA) and ND3 10389 genotype.

Conclusion: Mitochondria contribute to radiation sensitivity and genetic variations can be associated with late reactions to radiotherapy. Predictive markers of radiosensitivity should take into account mtDNA genetic variations in addition to variations in nuclear genes.

FUTURE RESEARCH DIRECTION

This research project has been completed. We started working on new project related to cervix carcinoma: HPV infection, genetic predisposition and biomarkers of response to chemo-radiation therapy.

PUBLICATIONS

Manuscripts

- Alsbeih GA, Al-Harbi NM, El-Sebaie MM, Al-Rajhi NM, Al-Hadyan KS, Abu-Amero KK. Involvement of mitochondrial DNA sequence variations and respiratory activity in late complications following radiotherapy. *Clinical Cancer Research*, Dec 1;15(23):7352-60, 2009 (Epub Nov 17, 2009).
  Indexed in MDLinx News (http://www.mdlinx.com) addressed to physicians and other healthcare professionals with summary and exclusive authors' comments.
- Jehan Z, Bavi P, Sultana M, Abubaker J, Bu R, Hussain A, Alsbeih G, Al-Sanea N, Abduljabbar A, Ashari LH, Alhomoud S, Al-Dayel F, Uddin S, Al-Kuraya KS. Frequent PIK3CA gene amplification and its clinical significance in colorectal cancer. *J Pathol.* Nov;219(3):337-46, 2009 (Epub Jul 7, 2009).
- Uddin S, Bavi P, Hussain AR, Alsbeih G, Al-Sanea N, Abduljabbar A, Ashari LH, Alhomoud S, Al-Dayel F, Ahmed M, Al-Kuraya KS. Leptin Receptor Expression in Middle Eastern Colorectal Cancer and its Potential Clinical Implication. *Carcinogenesis*, Nov;30(11):1832-40, 2009 (Epub Jun 11, 2009).
- Ghazi Alsbeih, Medhat El-Sebaie, Najla Al-Harbi, Khaled Al-Hadyan, Muneera Al-Buhairi, Martha Torres, and Nasser Al-Rajhi. Genetic polymorphisms, protein expression and complications to radiotherapy in Saudi cancer patients. *Journal of Medical Sciences*, May;2(2), 71-82, 2009.

Abstracts/Congress Proceedings

- Ghazi Alsbeih, Najla Al-Harbi, Muneera Al-Buhairi, Khaled Al-Hadyan. The association of MDM2 promoter T309G and TP53 G72C polymorphisms with radiosensitivity and cancer predisposition. 55th Annual Meeting of the Radiation Research Society (RRS), Savannah, Georgia, USA, 3-7 October 2009.
- Mehar Sultana, Zeenath Jehan, Prashant Bavi, Azhar Hussain, Ghazi Alsbeih, Nasser Al-Sanea, Alaa Abduljabbar, Luai H Ashari, Samar Alhomoud, Fouad Al-Dayel, Shahab Uddin, Khawla S Al-Kuraya. PI3K Gene Amplification is Frequent in Colorectal Cancer and Predicts Response for Adjuvant Therapy. 2nd KFSH&RC Residents' Research Day, 21 January 2009.

Clinical Dosimetry and Treatment Planning Unit

The Clinical Dosimetry and Treatment Planning Unit is charged with conducting radiation treatment plans and dosimetric calculations for a wide variety of malignant cancers and benign diseases. 2009 was a busy year for the section with the introduction of three new modalities in May 2009, Cyberknife, Tomotherapy and RapidArc. The number of patients utilizing the three different Intensity Modulated Radiation Therapy (IMRT) modalities have more than doubled, taking our annual number to over 300 patients treated with either Sliding Window IMRT, Tomotherapy or RapidArc technologies. As a direct result of this our number of man-hours has also increased significantly.

The Sliding Window IMRT, Tomotherapy, RapidArc and Cyberknife modalities all utilize Image Guided Radiation Therapy (IGRT) technologies to further improve the accuracy of these treatments, which provide better dose coverage of tumour sites while minimizing the dose to critical organs and normal tissues.

For 2010 our plan is to introduce CT planning for almost all patients regardless of their treatment intent (radical or palliative). This will also include a CT based, forward planned, IMRT technique for treating patients requiring whole Central Nervous System (CNS) treatment.

HEAD OF FACILITY

Michael Lim, CMD, ACT

STAFF MEMBERS

Baderaldeen Al Tazi, BSc *(RC Grant)*
Hind Al-Selham, MSc *(Returned from Study Leave August 2009)*
Ghadeer Nazer, BSc
Wedyan Safar, BSc, CMD
Lee Salter, BSc, CMD *(Resigned, November 2009)*
Paula Yates, RT(T), CMD
Ericka Venturina, BSc *(Grant Employee)*
Manal Awidah, BSc *(Grant Employee – Re-hired, December2009)*

ACTIVITIES	YEAR 2009
Monitor Unit (MU) Calculation/2-Dimensional Contour	519
Total Body Irradiation (TBI) Calculation	61
3-Dimensional CT Treatment Planning	1270
Stereotactic Radiosurgery/Radiotherapy (BrainLab)	2
Electron Cut-out Measurement	79
Intensity Modulated Radiation Therapy (IMRT)	243
RapidArc	29
Tomotherapy	29
Stereotactic Radiosurgery (Cyberknife)	52
TLD Dosimetry	64
Total Skin Electron Treatment (TSET)	2
High Dose-Rate (HDR) Brachytherapy	22
Low Dose-Rate (LDR) Brachytherapy	12
Clinical Consultation	48
Free-Hand Set-Up (FHSU)	14
TOTAL PROCEDURES	**2446**
PATIENTS	**1234**
MANHOURS	**10400***

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

TRAINING AND EDUCATION ACTIVITIES

- Hind Al-Selham, BSc, attained her Masters in Medical Physics from Surrey University, England. She returned to the Dosimetry Section in August 2009 and will move into the Radiation Physics section in 2010.

- Huda Al-Mohammed, BSc, CMD, attained her Doctorate in Radiography from City University, London, England. She returned to the Biomedical Physics Department in August 2009 to work in the Radiation Physics Section.

- Ghadeer Nazer, Bsc, plans to sit for the American Medical Dosimetry Certification Board examination in June 2010.

We continue to provide training in clinical dosimetry and treatment planning to physics undergraduate and graduate students from different universities within the Kingdom. We also continue to work as a greater team with our Radiation Physics Section colleagues to provide mutual training in the different areas related to clinical dosimetry.

STAFFING

Due to our continuing staff shortage, made worse by two senior staff resignations at the end of 2009, we continue to rely on our colleagues from the Radiation Physics Section as well as additional physics graduate Grant Employees to assist us in our workload. Recruitment of two medical dosimetrists are underway.

Gamma Irradiation Facility

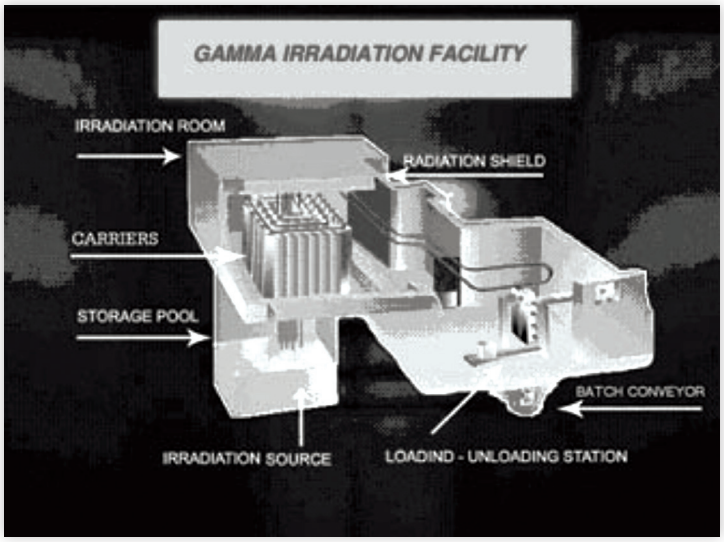
The Gamma Irradiation Facility (GIF) is one of the four core facilities of the Biomedical Physics Department in the Research Centre. The Facility is ISO 9001-2000 certified. It operates with three primary goals, namely: (1) to sterilize health care products for the needs of the KFSH&RC departments, and 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 FACILITY

Akram Al-Moussa, BSc

STAFF MEMBERS

Saad Bin-Jamaan, BSc
Edilberto Delos Reyes



CORE SERVICE ACTIVITIES

The activities of the Gamma Irradiation Facility in 2009 are as follows:

1. Continued to provide sterilization for hospital needs (Cyclotron kits and supplies of ART laboratory.
2. Provided gamma irradiation services for Master Degree students from different scientific institutes, with doing the necessary dosimetry for their samples.)
3. Research project with KACST on the film dosimetry has been completed, two scientific papers are expected to be published, a patent under consideration.
4. Bone bank of the KFSH&RC is opened and services of sterilization of bone grafts started. Special dosimetry procedures is prepared for this work, since it is done under refrigeration.

GAMMA RAY STERILIZATION

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

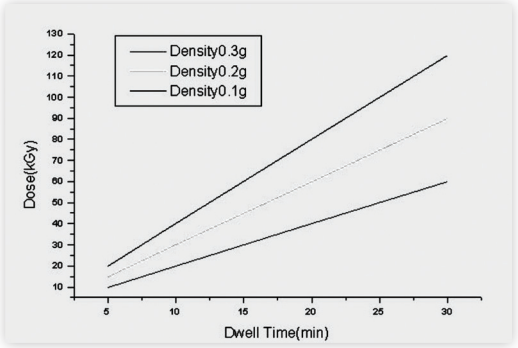


Figure 1: Relationship between Dwell Time and Dose for Materials of Different Densities.

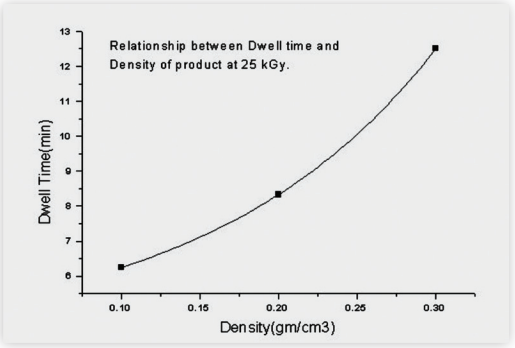


Figure 2: Relationship between Dwell Time (time of irradiation) and Density of Irradiated Materials.

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 maintains a thermoluminescent dosimetry (TLD) Laboratory that is licensed by the King Abdulaziz City for Science & Technology (KACST) making it the only laboratory in the Kingdom to meet national regulatory requirements. Leak tests for private companies were also provided by the section.

HEAD OF FACILITY

Fareed Mahyoub, MSc

STAFF MEMBERS

Celestino S. Lagarde, BSc
Ibrahim Al-Gain, BSc
Rami Al-Harbi, BSc *(RC Grant)*

Health Physics Activities

The table below summarizes the accomplishments made by the Health Physics Section for year 2009 in providing services to the KFSH&RC, to other facilities in the Kingdom of Saudi Arabia and surrounding countries in the Gulf region.

Task Descriptions	Quantity
Monitoring of Radiation worker for occupational doses	20812
Patients surveyed for radiation level	249
Patients rooms surveyed for radiation level	249
Patients rooms decontaminated	249
Leak test for sealed sources and radiation producing equipment	4
TLD badges irradiated for quality control of TLD readers of outside facilities	44
Consultative advice provided	6
Training courses & educational lectures provided	5

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 FACILITY

M. Gary Sayed, PhD, FACNM

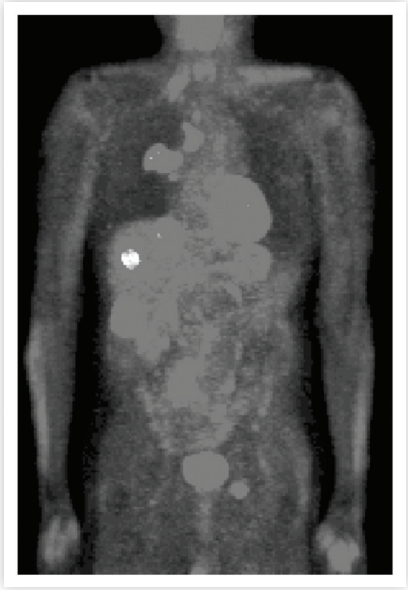
STAFF MEMBERS

Refaat Y. Al-Mazrou, MSc, MIPEM
Adnan Z. Al-Watban, PhD
Omer Demirkaya, PhD, DABSNM
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.

Molecular and Functional Imaging

With the conclusion of its inaugural year, the Molecular and Functional Imaging (MFI) has completed its strategic plan that culminated into a completed proposal for its foundation. The proposal included projected research priorities and endeavors as well as capacity building plans. The latter included funding proposals to the King Abdulaziz City for Science and Technology and the Ministry of Finance. The MFI mission is to conduct and stimulate research in the fields of functional imaging in close collaboration and cooperation with all inter- and intra-institutional stakeholders, including industry. The center endeavors to provide consulting expertise and education for the translation of basic research to clinical applications. It is committed to leadership and excellence in advancing the prevention, diagnosis and treatment of human disease through its tripartite mission focused on research, education and community service highlighted by cutting-edge research in the fields of molecular and functional imaging. As such, the MFI will strive to achieve the following objectives:

- Advance and create new knowledge through basic, translational and clinical research in a variety of scientific topics related to molecular and functional imaging, with the ultimate goal of improving human health.
- Promote multi-disciplinary biomedical education in the fields of functional imaging through enhancing the skills of today's researchers, preparing tomorrow's scientists and providing research exposure opportunities to young prospects.
- Serve the local community by addressing the issues and concerns of all stakeholders in the promotion and conduct for the center's objectives.

HEAD OF FACILITY

M. Gary Sayed, PhD, FACNM

STAFF MEMBER

Rami Niazy, PhD

Radiation Physics

The primary activities of the Radiation Physics Section are devoted to clinical physics and quality assurance services for cancer patients receiving radiation therapy. The section supports the treatment of nearly 1300 cancer patients per year through provision of approximately 3000 radiotherapy physics procedures annually. The Radiation Physic team played a vital role in the introduction of three major radiotherapy treatment modalities TomoTherapy, CyberKnife, and RapidArc into clinical practice at KFSH&RC in 2009. This made KFSH&RC the first institution in the whole world to have these treatment modalities in a single organization, and the first to have any one of these modalities in the region. First patients were successfully treated using all these modalities in May and July 2009. The Clinical Dosimetry and Treatment Planning Unit, which is a unit of the Radiation Physics Section, is charged with conducting radiation treatment plans and dosimetric calculations for a wide variety of malignant cancers and benign diseases. The Radiation Physics Section has experienced increase in workload over the past year due to the complexity and demanding of the introduced radiotherapy treatment modalities.

HEAD OF FACILITY

Belal Moftah, PhD, FCCPM

STAFF MEMBERS

Al-Kafi, Mohd Abdullah, MSc
Al-Mohammed, Huda, PhD
Al-Najjar, Waleed, PhD, ABR *(Adjunct Appointment)*
Ashmeg, Sarah, BSc *(On study leave)*
Chibani, Omar, PhD
El-Kaissi, Tarek, PhD
Hassan, Zeinab, PhD
Mahyoub, Fareed, MSc
Nobah, Ahmed, MSc
Santos, Rikka Maureen, MSc *(RC Grant)*
Shehadah, Mamoun, MSc
Yan, Xiang Sheng, MSc

RESEARCH PROJECTS

Project Title: Establishment of a Monte Carlo-based Clinical Dosimetry Center in Saudi Arabia.
RAC Project # 2060 026
Principal Investigator: *Belal Moftah*

Project Description

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

Progress

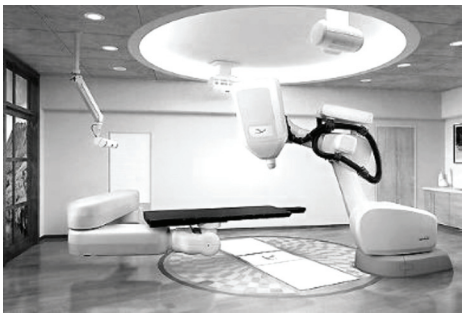
During last year, a computer cluster was acquired for the Monte Carlo project. Few more clinical parameters have been calculated and compared with measurements. Abstracts were presented to the World Congress on Medical Physics and Biomedical Engineering, held in September 2009, in Munich Germany. (KACST Project No. AT-25-85 - Approved funding: SR 652,000)

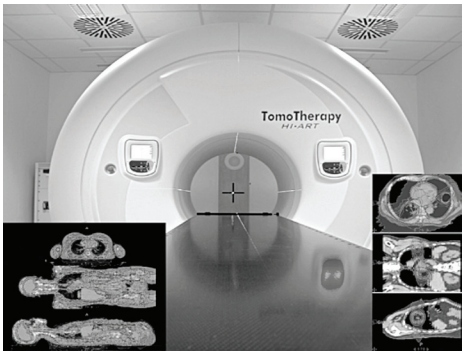
Project Title: Development of Novel 3D Gel Dosimetry System for Radiation Oncology Treatment Verification.
Principal Investigator: *Belal Moftah*

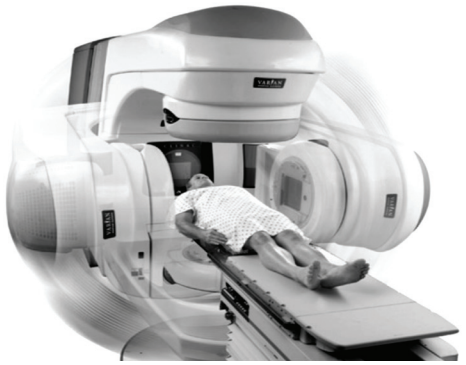
Project Description

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

Progress







A grant proposal was submitted to the KACST Advanced and Strategic Technologies program for funding (Budget requested SR 2.12 Million).

FUTURE CLINICAL RESEARCH DIRECTION

Project Title: Comprehensive Radiotherapy Treatment Planning Comparative Study.

Project Description

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

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

Progress

Research in preparation. The new innovative radiotherapy systems have been commissioned and are used on a daily basis for treatment planning of patients. A number of patients have been planned on several different treatment planning systems. A research proposal will be drafted and submitted.

Project Title: Incorporation of New Imaging Modalities (PET/CT and MRI Sim) Into Radiation Treatment Planning.

Project Description

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

Progress

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

PUBLICATIONS

INVITED PRESENTATIONS
(Presenting author)*

- Belal Moftah*, The Saudi Arabian Experience, IAEA Seminar on clinical training in radiation oncology as developed through RAS6038, First Coordination Meeting of TC project RAS/6/054, "Upgrading Medical Physics Services in ARASIA State Parties Through Education and Training (Phase II), Amman Jordan, June 7-11, 2009.
- Belal Moftah*, Implementation of Intensity Modulated Radiation Therapy (IMRT), KFSH&RC Experience, 4th International Saudi Medical Physics Conference, Saad Specialist Hospital, Khoubar, May 24, 2009.
- Belal Moftah*, Image-Guided HDR Endorectal Brachytherapy, International Conference on Innovative Approaches in Radiotherapy: Beyond Tomorrow, KFSH&RC, Riyadh, Saudi Arabia, March 9-12, 2009.
- Belal Moftah*, KFSH&RC IMRT Experience–Physical Aspects, International Conference on Innovative Approaches in Radiotherapy: Beyond Tomorrow, KFSH&RC, Riyadh, Saudi Arabia, March 9-12, 2009.
- Belal Moftah*, Opening Remarks, Opening Ceremony of the, International Conference on Innovative Approaches in Radiotherapy: Beyond Tomorrow, KFSH&RC, Riyadh, Saudi Arabia, March 9-12, 2009.
- Ahmad M. Nobah, Slobodan Devic, Sarah Ashmeg, Belal Moftah; Effect of different electron density geometric distributions on HU-ED calibration curves, Paper 7258-181 of Conference 7258; Disney Coronado Springs Resort Lake Buena Vista, FL, USA, February 7-12, 2009.

PRESENTATIONS AT CONFERENCES AND MEETINGS
*(Presenting author *)*

- Omar Chibani*, Belal Moftah, C-M Charlie Ma, Updated Beam Parameters for Monte Carlo Simulation of Five Varian Megavoltage Photon Beams (4, 6, 10, 15 and 18 MV), The World Congress on Medical Physics and Biomedical Engineering, Munich, Germany, September 7-12, 2009.
- Omar Chibani*, Belal Moftah, C-M Charlie Ma, Accelerated Dose Calculation Engine for Interstitial Brachytherapy, The World Congress on Medical Physics and Biomedical Engineering, Munich, Germany, September 7-12, 2009.
- Belal Moftah*, Ahmad Nobah, Verification and Quality Assurance of Intensity Modulated Radiation Therapy (IMRT) Treatments at KFSH&RC, Research Day 2009, Oncology Centre, KFSH&RC, Riyadh, May 6, 2009.
- Belal Moftah*, Omar Chibani, Abdullah Al-Kafi, Mohammad Al-Shabanah, Establishment of a Monte Carlo-based Clinical Dosimetry Center in Saudi Arabia (Project # 2060 026), Research Day 2009, Oncology Centre, KFSH&RC, Riyadh, May 6, 2009.

PUBLISHED ABSTRACTS

- Belal Moftah, Ahmad Nobah, Verification and Quality Assurance of Intensity Modulated Radiation Therapy (IMRT) Treatments at KFSH&RC, Abstract Booklet, Research Day 2009, Oncology Centre, KFSH&RC, Riyadh, May 6, 2009.
- Belal Moftah, Omar Chibani, Abdullah Al-Kafi, Mohammad Al-Shabanah, Establishment of a Monte Carlo-based Clinical Dosimetry Center in Saudi Arabia (Project # 2060 026), Abstract Booklet, Research Day 2009, Oncology Centre, KFSH&RC, Riyadh, May 6, 2009.

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-sight lectures, presentations, and verbal instructions for users of radiation. The Office keeps and maintains documents and records pertaining to inventory of radioactive materials, radiation incidents, authorizations and other documents on radiation safety. The RSO collaboratively works with Health Physics Section of the Biomedical Physics Department. It maintains linkages with other KFSH&RC safety committees, national agencies and with international bodies such as IAEA.

HEAD OF FACILITY

Fareed H. Mahyoub, MSc

STAFF MEMBERS

Ibrahim K. Al-Anazi, MSc
Celestino Lagarde, BSc

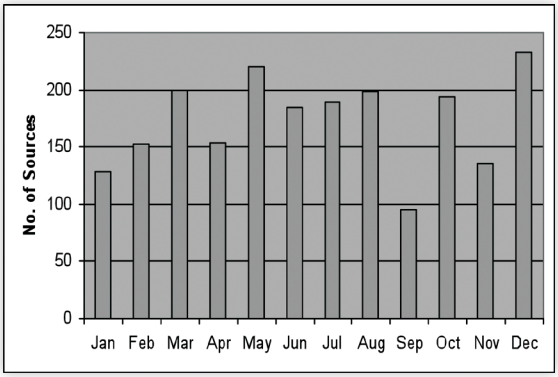


Figure 1: Graph showing the monthly out-going packages for year 2009.

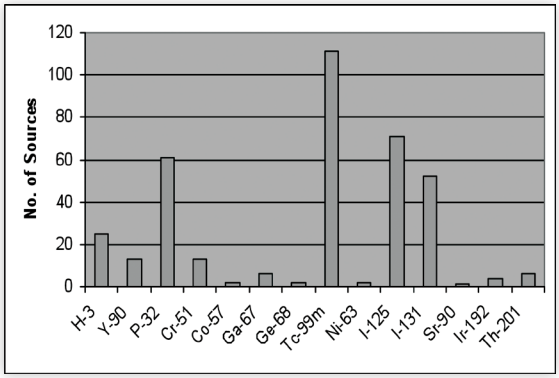


Figure 2: Graph showing the number of importedsources of radioactive isotopes in year 2009.

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 FACILITY

M. Gary Sayed, Ph.D., FACNM

STAFF MEMBERS

Abdalla Al-Haj, PhD
Nabil I'Qilan, MSc
Amal Al-Mutairi, BSc *(RC Grant)*
Nora Al-Mulhem, BSc *(RC Grant)*

ACTIVITIES

For the year 2009, 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 1161 radiation-measuring instruments were calibrated, inter-compared and acceptance tested. These instruments include 1062 survey meters, 98 pocket dosimeters, 0 radiotherapy dosimeters and 1 diagnostic dosimeters [Figure 2]. To ensure accuracy in its calibration, the SSDL participated in the IAEA and WHO annual postal dose audit for radiotherapy energy level of calibration where it obtained a very satisfactory result.

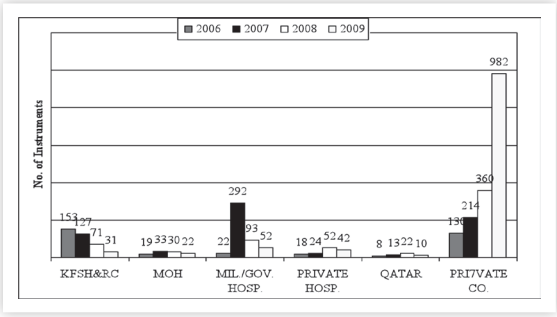


Figure 1: Graph showing the number of external facilities served and the number of instrument calibrated for each group by the SSDL.

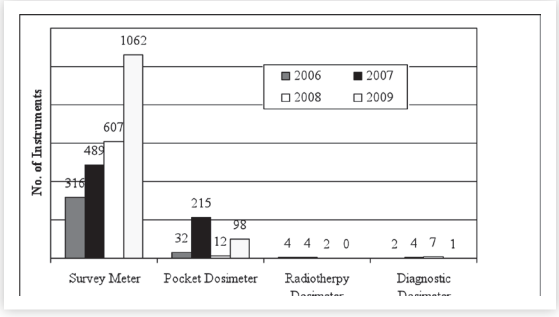


Figure 2: Graph showing the type and number of instruments calibrated.

The

BIOMOLECULAR RESEARCH PROGRAM

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 a result of a disease 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

OVERVIEW OF 2009 ACHIEVEMENTS

- Discovery of a novel regulatory pathway in cancer, which is auto-amplification of an RNA binding protein, HuR, which is important in growth of cancer cells. This finding is published in the journal "Oncogene".
- Discovery of a novel mechanism for the tumor suppression by a gene product known as RNase L. This finding was published in the journal Nucleic Acids Research.
- Development of Cloning-free regulated monitoring of reporter and gene expression as method platform. This led to a publication in "BMC Molecular Biology" which was labeled as highly accessed and "TECHNICAL ADVANCE' by Faculty of 1000 which highlights the top biomedical publications. This method was also previously filed in 2008 as a PCT patent application.
- Collaborative research with CNRS-UPS scientists in France (Dr. Morello and colleagues) resulted in two publications in PlosOne and Molecular Cellular Biology. These efforts include the expansion of our AU-rich RNA database methodology to the fruit fly (Drosophila) genome. This organism is considered a model for disease and drug research.
- Two PCT patent applications were filed in 2009 entitled: Granted (Issued) patent in EU entitled: "Method of Generating Translationally Active Linear DNA Molecules and Use Thereof in Array Formats."

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

- Edward Hitti, Suhad Al-Yahya, Maher Al-Saif, Peer Mohideen Linah Mahmoud, Stephen J. Polyak, Khalid S. A. Khabar. 2010. A Versatile Ribosomal Protein promoter-Based Reporter System for Selective Assessment of Post-Transcriptional Gene Regulation. *RNA*. In press.
- Nora Al-Suhaibani, John E. Hesketh, Perry J. Blackshear3, and Khalid S. A. Khabar* The RNA Binding Zinc Finger Protein Tristetraprolin Regulates AU-Rich mRNAs Involved in Breast Cancer-Related Processes. *Oncogene*. In press.
- Wijdan Al-Ahmadi, Maha Al-Ghamdi1, Latifa al-Haj1, Maher Al-Saif, and Khalid S. A. Khabar. 2009. Alternative Polyadenylation Variants of the RNA Binding Protein, HuR: Abundance, Role of AU-rich Elements, and Auto-Regulation. *Nucleic Acids Research*. 37(11):3612-24.
- 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*. 16;28(15):1782-91.
- 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, Borchi E, Khabar KS, Tempestini A, Lapucci A, Schiavone N, Nicolin 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. Invited 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.
- 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.

Invited Talks and Oral Presentations

- *Invited Talk:*. Al-Faisal University. The role of RNA binding proteins in chronic inflammation and cancer. March 2009.
- *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.

PATENTS / PATENT APPLICATIONS

1. International Patent Application. 2009. "Increasing Protein Expression in Eukaryotic Cells By Increasing RNA Stability."
2. International Patent Application 2009. "Methods for Producing Inducible and/or repressible Expression Active Linear RNA Interference Cassetes and Inducible and/or Repressible Expression Active Linear Gene Cassettes and Their Uses."
3. International Patent Application. November 17, 2008. PCT/EP2008/009712. "Expression Vectors Based on Modified Ribosomal Protein Promoters and Their Uses Thereof in Post-Transcriptional Assessment".
4. International Patent Application. June 27, 2008. PCT/EP2008/005278. "Cloning-Free Method of Generating Transcriptionally and Post-Transcriptionally Controllable Expression Active Linear Reporter Constructs."
5. Granted Patent (EU). Method of Generating Translationally Active Linear DNA Molecules and Use Thereof in Array Formats (EP, CA, US, 2007).

The

CENTRE FOR CLINICAL STUDIES AND EMPIRICAL ETHICS

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 and empirical studies and for training clinical/laboratory research professionals. The activities of the CCSEE are strategically chosen to: 1) build an appropriate, self-sustaining infrastructure, and 2) concentrate on projects of direct translational values. The Bioanalytical Laboratory of the CCSEE has been accredited by the College of American Pathologists (CAP) since May 2007. The gross income (fee from service) for the year 2009 was SR 184,000.00.

DIRECTOR

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

CO-DIRECTOR

Maha Al Saud, MD

MEMBERS

Abdelraheem Ahmed
Ahmed Yusuf, B.Sc
Eman Al-Gaai, RPh, CCRP, MHHA *(Flexible Employment Program)*
Hunida Abdulhameed, RPh *(Grant Funded – until 26 July 2009)*
Ma. Victoria G. Ventura
Nada Bin Hashim, RN *(Flexible Employment Program)*
Rajaa Hussein, RPh
Reem Al-Swayeh, RPh
Sahar Atalla, MBBCh, MS *(until 26 Sept 2009)*
Saleh Al-Dgither
Syed N. Alvi, PhD
Weam Al-Jasim, RPh
Yousef Al-Jawarneh, RN *(until 19 Nov 2009)*

PROJECTS/STUDIES

A. Drug Assay Development and Validation (8)

No.	Drug Name	Analysis Method	Volume (ml)	Matrix	Range (µg/ml)	Date Completed
1.	Piroxicame	HPLC-UV	0.10	Plasma	0.2-20	January 2009
2.	Glimepiride	LCMS/MS	0.50	Plasma	0.005-0.20	April 2009
3.	Methotrexate	HPLC-UV	0.20	Plasma	0.05-20	May 2009
4.	Atorvastatin	HPLC-UV	1.00	Plasma	0.02-1	May 2009
5.	Ketoconozole	HPLC-FL	0.25	Plasma	0.1-20	September 2009
6.	Mefenamic acid	HPLC-UV	0.50	Plasma	0.05-10	October 2009
7.	Ampicillin Trihydrate	HPLC-UV	0.25	Plasma	0.3-15	December 2009
8.	Cefazoline	HPLC-UV	0.25	Plasma	0.2-200	December 2009

B. Clinical (5)

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

Major Findings / Abstract

Background: The total effect of a medication is the sum of its drug effect, placebo effect (meaning response), and their possible interaction. Current interpretation of clinical trials' results assumes no interaction. Demonstrating such an interaction has been difficult due to lack of an appropriate study design.
Methods: We studied the interaction between drug and placebo effects, using a modified balanced placebo design. 180 adults were randomized to caffeine (300 mg) or placebo groups. Each group received the assigned intervention overtly and covertly in a randomized crossover design. Covert placebo and caffeine were presented as caffeine and placebo, respectively.
Main Outcome Measures: 4-hour-area-under-the-curve of systolic blood pressure; and energy, sleepiness, and nausea levels (on 100 mm visual analog scales), and caffeine pharmacokinetics (in 22 volunteers nested in the caffeine group) were determined. Caffeine drug, placebo, placebo-plus-interaction, and total effects were estimated by comparing covert caffeine to overt placebo, covert to over placebo, overt to covert caffeine, and overt caffeine to overt placebo, respectively.
Results: The placebo effect on area-under-the-curve of energy (mean difference) and sleepiness (geometric mean ratio) was larger than placebo-plus-interaction effect (16.6 [95% CI, 4.1 to 29.0] vs. 8.4 [-4.2 to 21.0] mm *hr and 0.58 [0.39 to 0.86] vs. 0.69 [0.49 to 0.97], respectively), similar in size to drug effect (20.8 [3.8 to 37.8] mm*hr and 0.49 [0.30 to 0.91], respectively), and its combination with the later was larger than total caffeine effect (29.5 [11.9 to 47.1] mm*hr and 0.37 [0.22 to 0.64] for energy and sleepiness, respectively). Placebo-plus-interaction effect increased caffeine terminal half-life by 0.40 [0.12 to 0.68] hr (P=0.007).
Conclusion: There may be a negative interaction between drug and placebo effects of a medication, which influences the interpretation of clinical trials. The placebo effect may increase active drug terminal half-life, a novel mechanism of placebo action. (ClinicalTrial.gov, number, NCT00426010.)

Status/Progress: Completed.

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

Status/Progress: On-hold.

Salivary Testosterone Level in Healthy Male Arabs.
RAC Project #: 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 spectrometery 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.

Status/Progress: Assay being validated.

Project Title: Age Related Clinical Presentation of Childhood and Adult Celiac Disease. A Retrospective Study on KFSH&RC Patients.
RAC Project #: 2091 034

Project Description

Celiac disease (CD) is a permanent inflammatory disease of the small intestine triggered by the ingestion of gluten-containing cereals in genetically predisposed individuals. The classic definition of celiac disease includes the following three features: villous atrophy; symptoms of malabsorption and resolution of the mucosal lesions and symptoms upon withdrawal of gluten-containing foods, usually within a few weeks to months. CD can develop during any point in life, from a newborn child to adult.

We plan to describe the different patterns of clinical presentation of patients diagnosed with Celiac disease at KFSH&RC, in various age groups and to explore the association between Celiac disease and other immunological and malignant diseases. This study will be a retrospective study that will be conducted at KFSH&RC. The study population will consist of all patients who had been referred for investigations of possible Celiac disease between 1998 and 2008. Patients will be identified through medical records of CD patients attending the nutrition Clinic at KFSH&RC. Special forms were developed by the investigators (Appendix I, II, and III), to collect the extracted information.

We believe that reporting the frequency of occurrence, various forms of clinical presentation, and complications of celiac disease will reveal the extent and severity of this disease, where early diagnosis is of utmost importance.

Status/Progress: RAC approved.

Project Title: Generic Formulations of Commonly-Used, Immediate-Release, Solid, Oral, Drugs in Saudi Arabia: Interchangeability and Post-Marketing Quality.
RAC Project #: 2071 001

Project Description

Generic formulations of prescription drugs can, through their relatively lower cost, improve healthcare as long as they maintain their registration-quality and public trust. On the other hand, the market availability of several generic formulations raises a concern regarding their interchangeability, despite being proven to be individually therapeutically interchangeable with their corresponding innovator formulation.

We propose to assess the quality and therapeutic interchangeability of generic formulations in the drug market of Saudi Arabia, using fifteen, commonly-used, oral, solid, immediate-release, and non-combinational drugs.

The following drugs have been identified from the Saudi National Formulary (September 2006) as having, among oral, immediate-release, non-combinational drugs, the highest number of formulations (they have each 15 to 47): ciprofloxacin, ranitidine, amoxicillin, paracetamol, atenolol, cephalexin, ibuprofen, diclofenac, metformin, omeprazole, metronidazole, enalapril, clarithromycin, amlodipine, and fluconazole. In the first set of studies and for each drug, a four-treatment, four-period, four-sequence, crossover bioequivalence study will be conducted on the innovator and three randomly-selected generic formulations. Each study will be designed to have a power of 0.9 to detect bioequivalence, and sampling and wash-out periods of at least 5 and 7 half lives, respectively. Individuals who are identified in the first set of studies as having the large intra-subject variation (bioequivalence parameters ratios of less the 80% or more than 120% for AUC) will be subjected to a second set of studies, in which 2 batches of the reference formulation (including the batch used in the first set of studies) and the generic formulation will be compared in a two-treatment, four-period, two-sequence, replicate design crossover bioequivalence study. Drug levels will be determined by an HPLC or LC-MS-MS method, locally-validated according to the Saudi Arabian Ministry of Health (MOH) and international guidelines. After log transformation, AUC and Cmax (non-compartmental model) of the formulations will be compared pair-wise by ANOVA. Pair-wise bioequivalence will be tested by 90% (and 95%) confidence interval of ratios and Schuirmann's two one sided t-tests for the 70-143, 80-125%, and 90-112% ranges.

The following (among others) will be determined: 1) the prevalence of generic formulations that are not bioequivalent to their innovator formulation, 2) the prevalence of the phenomena that two generics of the same innovator formulation are not bioequivalent to each other, 3) the percentage of individuals with large intra-subject variation despite the presence of average bioequivalence between the two formulations, and 4) how much of the large intra-subject variation in 3 above is true or related, in part, to product failure, random error, or subject-by-formulation interaction; and how it compares to intra-subject variability when two batches of the innovator formulation are compared. The studies will be conducted according to the regulations of the MOH and in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP) Guidelines, and Good Laboratory Practice (GLP) Guidelines.

The results of this project are expected to provide clinically- and regulatory-critical information on the post-marketing quality of generic formulations on the Saudi market and on the extent of the interchangeability of generic formulations in general.

Status/Progress: Submitted to the Long-Term Comprehensive National Plan for Science, Technology and Innovation.

EMPIRICAL ETHICS (7)

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

Major Findings/Abstract

Background: Available guidelines on disclosure of medical errors (ME) to patients and families have emerged largely in Western cultures. Their suitability for Islamic/Arabic cultures is not known.
Methods: 902 individuals attending the outpatient's clinics of a tertiary care hospital in Saudi Arabia were surveyed on disclosure of ME. Personal preference, and perception of norms and current practice regarding which ME to be disclosed (5 options: none, if associated with major, moderate, minimal, or no harm) and by whom (6 options: any employee, any physician, at-fault-physician, her supervisor, chief of staff, or chief executive director) were determined.
Results: Mean (SD) age was 33.9 (10) year, 47% were males, 90% Saudis, 37% patients, 49% employed, and 61% with college or higher education. The percentage (95% confidence interval) of respondents who preferred and perceived it normative to be informed of any-harm-ME, of no-harm ME, or by the at-fault physician were 60.0% (56.8 to 63.2) and 66.7% (63.7 to 70.0), 35.5% (32.4 to 38.6) and 30.4% (27.4 to 33.4), and 59.4% (56.5 to 63.0) and 57.2% (53.9 to 60.5), respectively. 68.1% (65.0 to 71.0) and 17.3% (14.7 to 19.8), respectively, believed that, as currently practiced, any-harm ME and no-harm ME are disclosed, and 34% (30.7 to 37.4) by the at-fault physician. There was significant correlation among preferences and perceptions of norms and current practice ($P<0.001$). In a forward stepwise regression, older age, female gender, and being healthy predicted preference of disclosure of no-harm ME; and younger age and male gender of not to be informed of ME. Female gender also predicted preferring disclosure by at-fault-physician.
Conclusion: We conclude that: 1) there is a considerable diversity in preference and perceptions of norms and current practice among respondents regarding which ME to be disclose and by whom, 2) most respondents preferred to be informed about harm-associated ME and by the at-fault physician, and 3) a high percentage preferred to and perceived it normative to be informed of no-harm ME especially among females and older individuals, and 4) there is considerable discrepancy between perceptions of norms and current practice.

Status/Progress: Completed.

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

Status/Progress: Recruiting (56% enrollment).

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

Status/Progress: Recruiting (18% enrollment).

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

Project Description

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

Status/Progress: Recruiting (70% enrollment).

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

Project Description

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

study is expected to provide physicians and policy makers with vital information on EOL priorities of Saudis. It will identify Saudi view(s) and contribute to global bioethics on EOL as well.

Status/Progress: Recruiting (10% enrollment).

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

Project Description

Protecting the rights and welfare of human subjects is essential in biomedical research, which is the sole responsibility of investigators recruiting human research subjects and shared with the institutional review boards (IRB), approving the study. The International Committee of Medical Journal Editors (ICMJE) established guidelines that oblige journal editors and publishers not to accept publications that do not conform to the principles of the declaration of Helsinki, but there is growing evidence that journals are not meeting these obligations.
Aims: Review the documentation of compliance with ethical guidelines, obtaining informed consent, obtaining IRB approval, and obtaining publication consent when publishing identifying information in published studies conducted in Saudi Arabia and published in Saudi journals.
Method: Used a specially designed data collection tool to verify the rate of reporting of: IRB approval, informed consent, publication consent, and compliance with ethical guidelines, from studies conducted in Saudi Arabia involving human subjects, published in Saudi medical journals, from January 1980-Decemebr 2007. Categories of study design as follows: retrospective or prospective medical chart review, retrospective or prospective studies on biological samples, interventional studies, surveys, interviews, and case reports. Descriptive statistics for frequencies and Chi square to study association of the degree of compliance were used with: journals, study design, publication's years, and the status of the journal (Index Medicus).

Status/Progress: Completed.

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

Status/Progress: Recruiting.

TRAINING AND EDUCATION

1. 10th Semiannual Clinical Research Professionals' Course, 2-13 May 2009 (66 CME hours with commendation by the AACME and 49 CME credit hours by the Saudi Council).
2. 11th Semiannual Clinical Research Professionals' Course, 24 Oct – 4 Nov 2009 (67 CME credit hours with commendation by the AACME and 49 CME credit hours by SCHS).
3. 3rd Semiannual LC&LCMS: Concept and Hands-On Training Course, 6-10 June 2009 (17 CME credit hours by the SCHS).

4. 4th Semiannual LC&LCMS: Concept and Hands-On Training Course, 7-11 November 2009 (17 credit hours by the SCHS).

PUBLICATIONS

- Eman A Al-Gaai and Muhammad M Hammami. Medical Chaperoning at a Tertiary Care Hospital in Saudi Arabia: Survey of Physicians. *Journal of Medical Ethics*: 2009;35:729-732.
- Rajaa Huseein and Muhammad Hammami. Validated Rabeprazole HPLC Assay in Human Plasma. *Analytical Science*: 2009.
- Rajaa Hussein and Muhammad Hammami. Fully Validated Diclofenac HPLC Assay. *Analytical Chemistry*: 2009;8(2).
- Rajaa Hussein and Muhammad Hammami. Rapid Analysis of Piroxicam Level in Microsample of Human Plasma by Fully Validated HPLC Assay. *Analytical Chemistry*: 2009;8(2).

PRESENTATIONS

Eight (8) abstracts accepted for presentation at UNESCO Islam and Bioethics International Conference, April 2010, Turkey.

- Al-Gaai E, Hammami MM. Medical Chaperoning at a Tertiary Care Hospital in Saudi Arabia: Survey of Physicians.
- Abdulhameed HE, Hammami MM, Hameed Mohamed EA. Disclosure of Terminal Illness: Governing Codes in Islamic & Arabic Countries.
- Al-Gaai, E, Al-Sayed H, Hammami, MM. Medical Chaperoning at a Tertiary Care Hospital in Saudi Arabia: Prevalence and Patient's Preference.
- Hammami MM. Comparison of Islamic Ethics and Contemporary Ethical Approaches.
- Hammami MM. Characteristics of Islamic Ethics.
- Hammami MM, Atalla S, AlQadery M. Which Medical Error to Disclose and by Whom? Public Preference and Perception of Norms and Current Practice.
- AlQadery M, Hammami MM, Abdulhammed H. Saudi Views on Consenting for Research on Medical Records and Leftover Tissue Samples.
- Hammami MM, AlJawarneh Y. Modeling Ethical Resolution: Mapping Points of Ethical Equilibrium.
- Syed Naseeruddin Alvi, Muhammad M Hammami. Rapid Determination of Caffeine Level in Human Plasma – A Validated Reversed Phase HPLC Assay Using Synthetic Plasma. Pittcon Conference, March 8-13, 2009, Chicago, Illinois, USA.
- Syed Alvi, Muhammad Hammami. Development and Validation of Reversed Phase HPLC Assay for the Determination of Caffeine Levels in Human Plasma. 2008 Annual Research Report, 16-18 March 2009, KFSH&RC.

The Department of

COMPARATIVE MEDICINE

Comparative Medicine

The mission of the Department of Comparative Medicine at the KFSH & RC is to foster knowledge and improve the health and well being of humans and animals by advancing research and training in comparative medicine and biology, and 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. This is accomplished by provision of the promotion of excellent and humane care and sharing of specialized expertise. An overarching goal is to insure a collaborative working environment based on integrity and trust.

The DCM is the animal resource center that provides service to all the scientist, physicians and surgeons in KFSH & RC and responsible for the husbandry and/or veterinary medical care post-surgical care, surgery, radiology, including x-ray and ultrasound, necropsies and a wide variety of technical services for all laboratory animals maintained for research, teaching, or surgical training.

Department of Comparative Medicine personnel are available to offer technical assistance to investigators and to perform procedures such as drug administration, body fluid collection (i.e., blood, urine), anesthesia, radiography, surgery and surgical assistance. DCM has a staff of veterinarians, technicians, nurses, support staff, adjunct veterinarians, and post doctoral veterinarians.

The department also assists, collaborates and conducts in-house research activities in areas pertinent to the Kingdom of Saudi Arabia such as tuberculosis, diabetes, cancer, genetic, urological disorders and cardiovascular diseases.

ACTING CHAIRMAN

Raafat M. El-Sayed, DVM, MVSc

ADMINISTRATIVE STAFF

Lorie Belarmino

THE COMPARATIVE MEDICINE DEPARTMENT CONSISTS OF:

A-The core facilities: consists of five sections

1. Laboratory Animal Facility
2. Experimental Surgery
3. Reproductive Biology & Transgenic Facility
4. Pathology & Diagnostic Laboratory
5. Radiology & Imaging unit

B-Research Units

1. Tuberculosis Research Unit
2. Microbial Immunology

ACHIEVEMENTS

a. Completion of the new modern DCM building.
b. Coordination with project Management Division for the pre-installation requirements of the essential needed equipments.
c. Re-organize and re-structure of the department

FUTURE GOALS

a. Strengthen the collaborations and links for research and training.
b. To be a worldwide recognized experiment surgical center
c. To work out and to prepare for the accreditation by the American Association for the Accreditation of Laboratory Animal Care International
d. To improve the newly established functional facilities such as Reproductive & transgenic, Pathology & Diagnostic laboratory and Radiology & Imaging facility.
e. To enhance the training for undergraduate and graduate students, technicians, nurses, scientists, physicians and surgeons.

Laboratory Animal Facility

The mission of the Laboratory Animal Facility 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 Center 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 provide purebred different animal species and mice that are genetically uniform and free from diseases for clinical and basic research undertaken by scientists and physicians. The Facility also ensures the prudent, ethical and scientific use of animals in accordance with both national and international guidelines. In addition, the staff of the facility provides veterinary and technical expertise to various KFSH&RC departments on a daily basis and provides high quality care, consultation in the safe, humane use of laboratory animals in research and education in compliance with international regulations and KFSH policies. All research protocols involving laboratory animals are reviewed by the animal care and use committee (ACUC).

HEAD OF FACILITY

Falah H. Al-Mohanna, DVM, MSc
Goran Matic, DVM

STAFF MEMBERS

Catalino L. Santos
Julius D. Mabborang
Wilfredo B. Antiquerra
Rolando G. Monzaga
Pio O. Oliveras
Ruben C. Delos Santos
Mona A. Saleh *(RC Grant)*
Bahaa Salem *(RC Grant)*
Baltazar Caducio

RESEARCH PROJECTS

The LAF is actively involved in providing laboratory animals and/or collaborating with several investigators at KFSH&RC as summarized below.

In-house Research Projects

a. RAC#2063 013. Signaling pathways involved in heatstroke pathogenesis.
b. RAC# 2050 012. Coagulation & fibrinolysis response patterns to severe heatstroke & its relation to inflammation & cell injury in baboon model: effect of tissue factors neutralization on outcome.
c. RAC# 2060 039. Modulating the Hypoxia Inducible Factor Sinaling Pathways as a Theraputic Modality to regulate Neovascularization related Retinopathies in mice.

Collaborative Research Projects

a. RAC# 2020 002. Photo biostimulation: laser effect in wound healing of diabetic & non diabetic rats. Dr. F. Al Watban, Dept. of Biological & Medical Research.
b. 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, follow up 2 recovered sheep.
c. RAC# 2030 088 Phase I&II. Myocardial Infract Model in Baboons. Dr. C. Mullangi. King Faisal Heart Institute, on going.
d. RAC# 2030 057. Investigation of BRAF mutation in thyroid carcinoma from Saudi population in mice. Dr. Y. Shi, Dept.of Genetics.
e. RAC# 2030 057. Gene Therapy for Anaplastic Thyroid Carcinma with a Single Chain Interleukin 12 Fusion Protein in vivo study. Dr. Y. Shi, Dept.of Genetics.
f. RAC# 2040 027. Synthesis of different radiofluorinated precursors for rapid Production of new PET radiopharmaceuticals. Dr. I. Al Jammaz, Dept. of Cycotron and Radiopharmaceticals (C&R).
g. RAC# 2042 001. Production if 'cold kits' for technitium-99m radiopharmaceuticals. Dr. I. Al Jammaz, Department of Cycotron and Radiopharmaceticals (C&R).
h. 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).
i. 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.
j. 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.
k. 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.
l. 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).
m. 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.

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 2009, LAF assisted research and training activities by providing various animals ranging from rodents to primates, maintained excellent health status of the mouse colony as well the successful production of large numbers of immuno- compromised scid mice, nude mice, NOD mice and more than 30 various strains of transgenic and knockout mice.

Animal facility staffs are committed to ensure humane and ethical care and use of animals involved in approved research to advance medical, biomedical and veterinary knowledge for the benefit of scientists, investigators, physicians, students.

	Mice	Mice Nude	Mice SCID	Transgenic	Rats	Rabbits	Hamster	Guinea pigs	Dogs	Sheep	Baboons
Used	3018	382	x	282	480	5	54	4	13	1	4
Inventory	786	238	200	689	512	10	94	2	53	2	57
Total	3804	620	200	971	992	15	148	6	66	3	61

TRAINING AND EDUCATIONAL ACTIVITIES

DCM provided training for high schools, under graduate students and post-graduate students 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

Training Program	# of Students	School/ College	Training Period
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	1 (PhD)	Girls College	Completed 2009
Provided basic surgery training to 4 undergraduate medical students from college of medicine, KSU.	4 (3 females + 1 male)	College of Medicine, KSU.	July-Aug. 2009 (1 month)
Provided one month summer training for 6 male high school students of Ibn Sena Program, King Abdulaziz and his Companion Foundation for the Gifted.	6 Males	Ibn Sena Program	July 2009 (1 month)
Future Scientist training	4 Males	High school Students	Aug. 2009
TOTAL	**15**		

PUBLICATIONS

- M. DeNiro, A. Al-Halafi, FH. Al-Mohanna, O. Alsmadi, and FA. Al- Mohanna. Pleiotropic Effects of YC-1 Selectively Inhibits Pathological Retinal Neovascularization and Promotes Physiological Revascularization in a Mouse Model of Oxygen-Induced Retinopathy. *Mol Pharmacol*. [Epub ahead of print] Dec 14, 2009; doi: mol.109.061366.
- M. DeNiro, A. Al-Halafi, F.H. Al-Mohanna, O. Alsmadi, F.A. Al- Mohanna. Dual Targeting of Retinal Vasculature: YC-1 Selectively Mediates Retinal Vascular Remodeling in the Ischemic Retina and Exhibits Potent Inhibitory Effects on Retinal Neovascularization in a Mouse Model of OIR. *ARVO*, FL, USA, May 2009
- M. DeNiro, A. Al-Halafi, F.H. Al-Mohanna, O. Alsmadi, F.A. Al-Mohanna. Scientific work was featured on the JOURNAL COVER. Molecular Pharmacology, March.2010. *doi:mol*.109.061366.
- M. Deniro, Al-Mohanna F.H, Al-Halafi A, Alsamadi O, Al-Mohanna FA. Inhibition of Inducible Nitiric Oxide Synthase Enhances Physiological Revascularization and Reduces Pathological Neovascularization in a Mouse Model of Retinopathy of Prematurity. Submitted to *Nitric Oxide Journal*.

Experimental Surgery

The primary function of Experimental Surgery 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.

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 as Microsurgery, Laparoscopy and Endoscopy, Bowel Anastomosis, Vascular Surgery, General Surgery, Life Support Training and Difficult Airway Management.

A modern surgical theatre, fully equipped with state of the art equipments and all the auxiliary facilities for general surgery, cardiovascular surgery, laparoscopic and neuro-surgery to ensure the success of all surgical procedures.

HEAD OF FACILITY

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

STAFF MEMBERS

Falah H. Al-Mohanna, DVM
Goran Matic, DVM
Farraj Al-Samer
Ludivina A. Apilado
Sahar I. Salem
Merfat A. Elyan
Saad Al-Durgham

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:

a. Microsurgery
b. Laparoscopy
c. Endoscopy
d. Bowel Anastomosis
e. Vascular Surgery
f. General Surgical procedures
g. Difficult Airway Management
h. Life Support Training

FACTS AND FIGURES

Workshops in Collaboration with Hospital Departments, Performed in Year 2009

Training & Workshops	Details
Microsurgery, Intensive Course, each course 5 days per week	1 course, 40 rats, 4 participants, 2 Instructors
Microsurgery for KFSH & RC users, students, residents and surgeons	120 Rats, 50 participants
Laparoscopy and Bowel Anastomosis & General Surgery procedures for Residents, Two seasons.	1 workshop, 4 dogs, 36 participants, 6 Instructors, 2 OR nurses
Life Support Training Fundamental of Critical Care Support	30 participants, 1 sheep
TOTAL	***Participants : 90, Instructors: 10, Dogs: 4, Sheep:1, Rats: 160***

Training & Workshops / RAC #	Principal Investigator / Department	Date	# of Participants	Animals Used
Bowel Anastomosis, general surgery procedures and Laparoscopy RAC # 2032 002	Dr. Luai Ashaari, & Dr. O'Regan	31 Dec.2009, Animal Lab & Dry Lab	36 participants, 6 instructors 2 OR nurses+ 7 LAF staff (in 2 sessions)	4 dogs
Life Support Training Centre: Fundamental of Critical Care Support	Dr,Sulaiman Al Hosaini	2009	20-30 participants	1 sheep
Microsurgery Intensive Course RAC # 2022 008	Dr. Essam Al Shail / Dept. of Neurosciences	7-11 March 2009 Five days	4 participants, 2 instructors	40 rats
			66 participants, 6, instructors, 7 CMD staff	4 Dogs, 1 Sheep, 40 Rats

Microsurgery Weekly Training

Microsurgery RAC # 2022 007	**Drs.Hashem Fouad & Ali Al Malaq, Plastic Surgery.**	**Every Wednesday**	**5 participants, 1 instructor**	**70 Rats**
Microsurgery Training RAC# 2082 001	**Dr. Raouf Seyam, Department of Urology**	**Every Sunday**	**1-2 participants**	**35 rats**
Microsurgery Training RAC# 2082 003	**Orthopaedic Surgery**	**Occasionally Every Monday**	**2 participants**	**15 rats**

TRAINING AND EDUCATIONAL ACTIVITIES

Training Program	Animals Used	Training Period
Provided basic surgery training to 4 under graduate medical female students from college of medicine, KSU.	Small & large animal	Aug 2009, (1 month)
Provided one month summer training for 10 males high school students of Ibn Sena Program, King Abdulaziz and his Companion Foundation for the Gifted and Future Scientist programs	Mice/Rats	July 2009, (1 month)
Riyadh Girls High School, 60 students per time	Small & large animals	Demonstration 2-3 hrs every, Monday, for 2-3 times June 2009

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, and Urology as summarized below:

Research Project/P.I./Department	No. of Animals Used	RAC Approved No. of Animals
RAC# 2050 032. The Effect of α 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# 2030 088 Phase I&II. Myocardial Infract Model in Baboons. Dr. C. Mullangi. King Faisal Heart Institut. Follow up	5, Cardiac procedures, inject of stem cells	5 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

FUTURE PLANS

a. To establish a worldwide training centre in collaboration with the Departments of Surgery, Neuroscience Urology, and Cardiovascular Surgery at King Faisal Specialist Hospital and Research Centre.

b. Furthermore, work is in progress to establish laparoscopic surgical theatres Linked by an interactive multimedia teaching system, which displays different kinds of images, surgical laparoscopic procedures and endoscopic view.

c. To establish a simulator dry lab for training general suture, laparoscopy and microsurgery.

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 FACILITY

Sahal Al-Hajoj, PhD

STAFF MEMBERS

Bright Varghese
Ruba Al-Omari
Mais Al-Herbawi
Raniya Al-Moneim

RESEARCH PROJECTS

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 and 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-Raabiah, 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

The project has started on July 2009. The plan is to collect isolates from all TB centres around the country for one year. The analysis of the isolates should be carried out as the collection goes on. So far 1000 isolates have been collected and almost 50% of these isolates were treated for Drug susceptibility testing.

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

We were able to recruit 60 patients. The recruitment was carried out by our co-investigators working in the renal transplant unit. The blood sample of recruited patients was subjected to interferon Gamma investigation. The final analysis of such investigation can be performed only after the completion of the study.

PUBLICATIONS

- Al-Hajoj Sahal Abdulaziz: Molecular strain typing of Mycobacterium tuberculosis isoltes to dedct Cross-contamination events- Prposed modifications to prevent its recurrence.*SaudiMed J* 2009; Vol30 (12) 115-119.
- Al-Hajoj Sahal Abdulaziz: Can we change the way we look at BCG vaccine? *Ann Thorac Med* 2009, April-June, Volume 4, Issue 2.
- Van Ingen Jakko; Al-Hajoj Sahal A M; Boeree Martin; Al-Rabiah Fahad; Enaimi Mimount; de Zwaan Rina; Tortoli Enrico; Dekhuijzen Richard; Van Soolingen Dick *Mycobacterium riyadhense sp. nov.*, a non-tuberculous species identified as *Mycobacterium tuberculosis* complex by a commercial line-probe assay. *International Journal of Systematic and Evolutionary Microbiology* 2009;59(Pt 5):1049-53

FUTURE RESEARCH DIRECTION

We are hoping to put together the data generated over the last 4 years to build a proper data base for all types/ clades of TB present in Saudi Arabia together with the epidemiological data and their drug resistance profile. This data base should be available for all health authorities to enable them to tackle the problem based on such solid data.

International Collaboration:

1. Dr. Dick van Soolingen, 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 Guadaloupe, Institut of Pasteur de Guadeloupe and Paris.
4. Dr. Timothy McHugh, UK, Department of Medical Microbiology, Royal Free University College Medical School, London.

Microbial Immunology

The research thrust at the laboratory of Microbial Immunity is currently focused on the host response to 2 major infectious diseases prevalent in KSA, namely brucellosis, and tuberculosis. Elucidation of the regulatory mechanisms involved in microbial pathogenesis and immunity are pivotal towards the development of rational vaccine and/or drug discovery against these two deadly diseases. For brucellosis, our research highlighted the importance of transforming growth factor- beta (TGF-β) in the subversion of immunity. Our data showed that abundance of TGF-β secretion may underlie the depressed function of T-cells in patients with chronic brucellosis (Microbes and Infection 11: 1089-1096, Dec 2009). For tuberculosis, however, our data showed the predominance of growth factors (PDGF, VEGF, TGF-β, and EGF) in plasma and peripheral blood mononuclear cells (PBMC) of TB patients at the time of disease diagnosis. The production and expression of these growth factors had significantly reduced after the treatment of patients with antituberculosis drugs. The molecular basis of effective therapy and improved immunity in TB patients correlated well with iNOS overexpression and enhanced IFN-γ production in tuberculous PBMC-stimulated with culture filtrate protein (CFP) derived from Mycobacterium tuberculosis (MTB).

HEAD OF FACILITY

Mohamed G. Elfaki, PhD

RESEARCH PROJECTS

Active Project

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 (T.B.), 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 T.B. In this study, we proposed a two-fold approach to investigate the regulatory role of cytokines in patients with tuberculosis. In the first approach, cytokines level in plasma samples of patients with pulmonary and extra-pulmonary T.B. will be studied by ELISA. In the second approach, the patterns of cytokine gene expression and protein level will be studied *in vitro* by using mononuclear cells as target cells. The threshold detection of cytokines in both systems would provide insights into possible means of immune intervention as well as in the prediction of T.B. status. Thus, the compendium knowledge of cytokines profile would enhance our judgment about the prognosis of T.B. and pave the way towards future use of cytokines as adjuvant in the treatment regimen of tuberculosis. Additionally, anticipated differences in cytokine responses between pulmonary and extra-pulmonary T.B. might be of diagnostic value at certain stages of disease progression.

Progress

The role of cytokines and growth factors in tuberculous patients has been delineated. Despite a low production of cytokines-associated protection, the production and expression of growth factors predominate in patients with active pulmonary tuberculosis. The level of growth factors had significantly reduced after the treatment of patients with antituberculosis drugs. Therefore, the plasma level of growth factors expression before and after therapy might be used as a good prognostic marker in determining the outcome of tuberculosis. The anticipated improved immunity of tuberculous patients that underwent therapy was studied by the expression of iNOS, a major generator of nitric oxide that halts the multiplication of *Mycobacterium tuberculosis* (MTB). Our data showed that iNOS was significantly overexpressed by RT-PCR in RNA isolated from tuberculous PBMC-stimulated with culture filtrate protein (CFP) derived from MTB. The iNOS expression correlated well with IFN-γ production in tuberculous PBMC-stimulated with CFP. Taken together, these results suggest that the enhanced production and expression of growth factors in tuberculous patients might be implicated in the host response to MTB infection. The overexpression of iNOS in PBMC-stimulated with CFP protein suggests that this antigen is important in MTB immunity.

Pending Projects

1. Modulation of the Host Cell Proteome in Patients with Active Brucellosis; Submitted December 2009 to KACST for funding.
2. Novel approach for the delivery of vaccine against Brucella melitensis using biodegradable poly (D, L, lactic-co-glycolic acid) nanoparticles; The project will be sponsored by KSU biotechnology funds.

PUBLICATIONS

- Elfaki, M.G., Al-Hokail, A.A., Alaiya, A.A., Al-Neshmi, A., and Marie, A. (2010). Proteomic analysis of tuberculous peripheral blood mononuclear cells in patients with active pulmonary tuberculosis. 110th General Meeting of the American Society for Microbiology, San Diego, CA, U.S.A. (May 23-27, 2010). Accepted.
- Elfaki, M.G., and Al-Hokail, A.A., 2009. Transforming growth factor β production correlates with depressed lymphocytes function in humans with brucellosis. *Microbes and Infection.* 11:1089-1096.

- 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. Presented at the 109th General Meeting of the American Society for Microbiology, Philadelphia, PA, U.S.A. (May 17-21, 2009).
- 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. Presented at the 109th General Meeting of the American Society for Microbiology, Philadelphia, PA, U.S.A. (May 17-21, 2009).

Pathology and Diagnostic Laboratory Medicine

The Diagnostic Laboratory is a newly formed section for the purpose of basic disease surveillance and diagnosis and will offers clinical laboratory services to investigators in the biomedical research.

The P&DLM will provide a complete animal health screening, full diagnostic and genotyping services for all laboratory animals used in biomedical research to the veterinarians monitoring the health status of animals and to support numerous research projects from scientists using animal models for approved research projects. These services are divided into three major areas: Clinical Pathology (perform hematology, clinical chemistry, parasitology and bacteriology), Molecular Pathology (Serology/Immunology, PCR), and Histopathology.

HEAD OF FACILITY

Steve Bobis, DVM

STAFF MEMBERS

Abdulrahman Al-Zuhaifi
Hala Ahmed Abddelrahman
Mona Saleh

Radiology and Diagnostic Imaging Facility

The section is a newly formed imaging facility. DCM maintains radiography facilities for diagnostic and experimental use in biomedical research. It aims to facilitate animal research in the fields of molecular and functional imaging. It will also assist in diagnosis and treatment of animal diseases.The section will include State-of-the-art imaging facilities for digital radiology, ultrasound, 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, IVES (Bioluminescence, Fluorescence), Angiography (fluoroscopy) and Ultrasonography.

HEAD OF FACILITY

Goran Matic, DVM
Falah H. Al-Mohanna, DVM, MSc

STAFF MEMBERS

Jullius Mabborang

Reproductive Biology and Transgenic Animal Facility

This section is a newly formed facility. The purpose of Reproductive Biology (RB)is to provide access to reproductive animal technology to investigators in an efficient and effective manner by using IVF and to improve the techniques involved in Reproductive Technologies, study fertilization mechanisms and improve the technical skills; This section will provide Embryo Cryopreservation (freezing of mouse embryos for preservation in liquid nitrogen, backup to production colonies, minimize genetic drift over long periods of time, preserve animal models, and establish ova and semen animal bank.

The Transgenic Animal Facility (TAF) aims to generate, develop, and maintain various animal models such as transgenic knock-in and knock-out lines for a number of important human diseases such as neurodegenerative disorders, diabetes, muscular dystrophy, cardiovascular diseases, genetic and reproductive disorders, many of these transgenic animals represent genetic models for human diseases, which will help the researcher to find treatment strategies for such diseases. This section will provide different services such as injection of DNA into mouse eggs for the production of transgenic mice or embryos and injection of embryonic stem cells into blastocysts for the production of chimeric mice.

HEAD OF FACILITY

Abdallah Assiri, DVM, PhD

The Department of

CYCLOTRON AND RADIOPHARMACEUTICALS

Cyclotron and Radiopharmaceuticals

Radiopharmaceuticals are the key components of a viable nuclear medicine practice. Cyclotron and Radiopharmaceuticals Department (C&RD) manufactures and supplies a wide range of radiopharmaceutical products to nuclear medicine centers within the Kingdom and abroad, facilitating and enhancing the diagnostic imaging and radiotherapy services.

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

Radiopharmaceutical manufacturing: Radiopharmaceuticals are the products labeled with radioactive isotopes, and are the key ingredients in practice of nuclear medicine. C&RD is the only facility of this kind within the geographical region manufacturing these specialty products. 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. Manufacturing complies with guidelines for Good Manufacturing Practices (GMP) and the ISO 9001:2008 Quality Management System for further quality enhancement.

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

CHAIRMAN

Manhar M. Vora, PhD

DEPUTY CHAIRMAN

Ibrahim Al-Jammaz, PhD

ADMINISTRATIVE STAFF

Nora B. D'Souza
Jhonna L. Canicosa

DEPARTMENT STAFF

Cyclotron Operation
Faisal Al-Rumayan,PhD
Engr. Salam Rahma
Engr. Ahmed Al-Gaith
Engr. Willem Van Heerden
Eugene Vorster
Suliman Al Hoban

Radiopharmaceuticals Production
Suliman Al Yanbawi
Marsood Ahmad
Barakat Al-Kenani
Subramani Narasimhan
Hussien Al-Dossari
Mohammed Al Subeiy
Abdulrahman Al Omar
Mohammed Al Enazi
Reynaldo Lapuz
Ibrahim Al Olayan

Quality Control/Quality Assurance
Abdulrahman Al Rabiah
Omar Al Shammari
Sonny Wahab
Lafi Al Enazi
Nora Kato
Evelyn delos Reyes
Mohamamed Shoaib Shawoo

Precision Machine Shop
John Fulton Schneider
Saad Ibrahim Al-Olayan
Mohammed Mansour

ACCOMPLISHMENTS YEAR 2009

Radiopharmaceutical manufacturing: In the Year 2009, 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 GMP and the ISO 9001:2008 Qualify Management System.

A major expansion project is in progress, 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 the Technitium-99m generator which is a workhorse for diagnostic imaging. Upon completion of the project in December 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, senior scientists have been appointed to co-author a number of manuals in book format for benefit of the cyclotron radionuclides and radiopharmaceuticals manufacturers. Four of these books were published during the year with twobeing in the final stage of editing. Moreover a training module is being developed for WEB-based training in production of radioisotopes and radiopharmaceuticals.

Two PhD students graduated under the supervision of Senior Scientists

HIGHLIGHTS OF THE ACCOMPLISHMENTS FOR THE YEAR 2009

Radiopharmaceuticals Production Related:

- 18,769 units of radiopharmaceuticals distribution to 40 nuclear imaging centers in the Kingdom and abroad.
- SAR 11,059,692 revenues generated from distribution of radiopharmaceuticals.
- 98.3% process success rate in manufacturing radiopharmaceutical products.
- Achieved objectives of the ISO 9001:2008 Quality Management System, including customer satisfaction rate of 93.4%.
- 0.9% non-conformities: ISO 9001:2008 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 cyclotron isotopes and radiopharmaceuticals (two are published to-date)

Radiotracer Research Related:

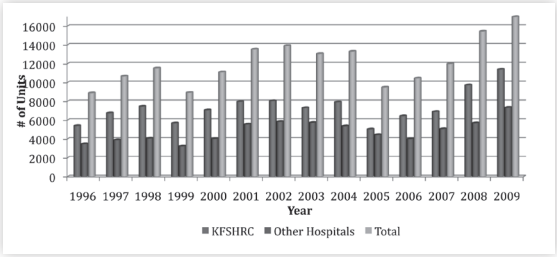
- Eleven active research projects
- Three Grant funds (KACST funded, over 3-4 years)
- Two Publications in peer-reviewed journals
- Eight abstracts and presentations

FUTURE DIRECTIONS

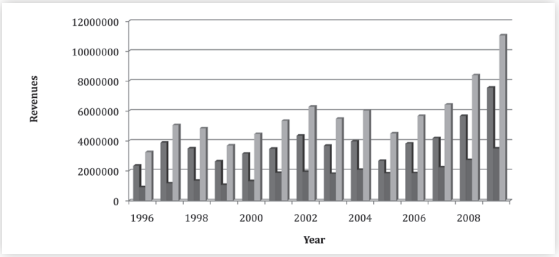
With an ultimate aim of becoming a single source of all radiopharmaceutical needs of the Kingdom, an ambitious project entailing physical expansion of the C&R Department is in final stage of construction and commissioning. Upon completion of this project in December 2010, we expect to achieve our ultimate 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



Total Number of Units Distributed
(1996 – 2009)



Total Revenues
(1996 – 2009)

Radiopharmaceuticals Research

Molecular imaging is defined by the Society of Nuclear Medicine as “the visualization, characterization and measurement of biological processes at the molecular and cellular levels in humans and other living systems”. The progress and utilization of nuclear molecular imaging will be sustained by developing novel, selective and sensitive radiotracers based on proven physiological, biochemical and pharmacological concepts. For this reason our research has focused on radiolabeling bioactive molecules such as peptides, peptidomimetics and drugs, and to explore their potential application as diagnostic or therapeutic radiopharmaceuticals. Ideally these target molecules must be labeled with isotopes of natural elements such as C-11, N-13 or O-15. However, the short half-lives of these isotopes place limitations on their application. Nonetheless F-18 has been an excellent substitute for these elements. The replacement of a hydrogen or hydroxyl by F-18 in some cases has resulted in better radiotracers than those with the natural isotopes. The prerequisite of these investigations require the development of efficient, fast and simple chemical reactions, optimizing analytical methods and techniques for the product and finally performing the requisite in vitro and in vivo tests including imaging to prove their eventual utility in humans.

Radiohalogenated peptides and drug molecules are potential radiotracers targeting a gamut of diseases including cancer, infection and inflammation, apoptosis, tissue and organ rejection, diabetes, etc. Additionally, the kinetics of most ligand-receptor interactions favors radiolabeling with Tc-99m and other short-lived radionuclides such as Cu-64 and I-124.

Increasing demand for nuclear medicine imaging procedures implies that old methods must be improved and new ones sought for the production of radionuclides and radiopharmaceuticals. Initial effort to produce and evaluate other radionuclides will be undertaken in the near future.

HEAD OF FACILITY

John K. Amartey, PhD

STAFF MEMBERS

Ibrahim Al-Jammaz,PhD
Subhani Okarvi, PhD
Mohammed Al-Qahtani, PhD
Basem Al-Otaibi

RESEARCH PROJECTS

1. Preparation and Characterization of Radiolabeled Bombesin Peptide analogs Targeting Human Cancers: A Foundation stone for Molecular Imaging program (KACST #AT 25-06, RAC# 2030-058). *PIs:* Al-Jammaz I; Okarvi SM; *CoIs:* Bin Amer S; Amartey JK. (Active).
2. Study of Protons Reaction with Natural Krypton Target for Production of 81Rb-81mKr Generator at Ep <27 MeV (RAC#2070 016, PhD student). *PI:* Al-Jammaz I; CoIs: Azzam A; Miliebari S; Al-Mogren J (Completed).
3. Synthesis and characterization of new rhenium and technetium complexes as potential radiopharmaceuticals (RAC# 2070 019, PhD student). *PI:* Al-Jammaz I; *CoIs:* Mahfouz R; Al-Hokbani N. (Completed).
4. Standardized High Current Liquid and Gas Targets for Cyclotron Production of Diagnostic and Therapeutic Radiopharmaceuticals. (IAEA # SAU13483, RAC# 2050 027). *PI:* Al-Jammaz I; *CoIs:* Miliebari S; Al-Yanbawi S; Rahma S; Van-Heerden W (Completed).
5. Vaginal Tablets as Novel Methotrexate Target Regiment for Safe Remission of Uterine Tumor. (RAC# 2080 048) *PI:* AlJammaz I., *CoI:* Omar S (Active).
6. Development of ^{18}F-labeled Radiopharmaceuticals (beyond [^{18}F]-FDG) for Use in Oncology and Neurosciences, (IAEA SAU-15331, RAC# 2080 028). *PI:* AlJammaz I., *CoI:* AlRabiah A., AlYanbawi S. (Active).
7. Study of the Anti-Cancer Properties of PAC (a Novel Curcumin Analogue) *In Vitro* and *In Vivo*. (RAC#2080 027). PI: Aboussekhra A., Co-I: AlJammaz I. (Active).
8. Preparation, radiolabeling and in vitro and in vivo characterization of tumor-antigens-derived peptides for the detection of breast and other cancer (KACST project# M-S-12-2). *PI:* Okarvi SM; *CoI:* Al-Jammaz I. (Active).
9. Synthesis and initial evaluation of [^{18}F]-VEGFR-2 antagonist as a potential tracer targeting angiogenesis (RAC# 2070-011). *PI:* John K. Amartey; *CoI:* Futwan Al-Mohanna (Completed).
10. Evaluation of radioiodinated laminin-1 derived peptide antagonist that blocks angiogenesis and tumor growth (RAC# 2060-001). *PI:* Mohammed H. Al-Qahtani; *CoI:* John K. Amartey. (Completed).
11. Radiolabeling and Preliminary Evaluation of laminin-1 derived peptide antagonist that blocks angiogenesis and tumor growth. ("KASCT # ARP-29-15; RAC # 2080 047). *PIs:* Mohammed H. Al-Qahtani; *CoI:* John K. Amartey. Commencement on 15 April 2010.

FUTURE RESEARCH DIRECTION

The results obtained so far on these projects are encouraging. In the development of the prosthetic groups for radiohalogenation we have successfully prepared compounds labeled with either [^{18}F] or [$^{123/125/131}$I]. These have been attached to selected molecules with moderate to high labeling efficiencies. With this technique in hand we are in a position to radiohalogenate specific biomolecules targeting cancer, infection and inflammation, etc. Biological evaluations of some of the promising radiotracers are ongoing to fully establish their utility. Additionally, we continue to explore methods that are high-yielding, robust, and reproducible and also reduce the radiohalogenation reaction times. The promising radiolabeled compounds will be modified and additionally conjugated to near infrared (NIR) wavelength emitting dyes to facilitate nuclear and optical imaging. Bifunctional derived radiometal chelating experiments with Tc-99m and other radiometals shall be pursued. In nuclear and radiochemistry target re-design and better electroplating to improve cooling during irradiation will be investigated to increase radionuclide yield. Therefore we intend to continue to intensify our efforts in these areas and to develop and produce other short and medium-lived radionuclides (i.e. Cu-64 and I-124) to further our overall goals.

PUBLICATIONS

Book Chapter

- AlJammaz I. Water targets-Product Considerations In Cyclotron Produced Radionuclide: Operation and Maintenance of Liquid and Gas Targets. (In press 2010).
- S.M. Okarvi, I.A. Jammaz: Design, synthesis, radiolabeling and *in vitro* and *in vivo* characterization of tumor-antigens and antibody-derived peptides for the detection of breast cancer. *Anticancer Res.* 29: 1399-1410 (2009).

Abstracts and Presentations

- Mohammed H. Al-Qahtani and John K. Amartey. Preliminary Radiolabeling and Evaluation of laminin-1 derived peptide antagonist. *Nuclear Medicine Communication* 30 (5); p 405, 2009.
- S.M. Okarvi. Preparation and evaluation of a Tc-99m-labeled bombesin peptide derived from the universal sequence for targeting bombesin receptor-expressing tumors. *Eur. J. Nucl. Med. Mol.* Imaging. 36: S221 2009.
- Al Jammaz. Positron Emission Tomography (PET) Radiopharmaceuticals: [^{18}F]-FDG and Beyond, 3rd Gulf Nuclear Medicine, Kuwait, March 2009.
- I. Al Jammaz. Standard of Practice Specific to Positron Emission Tomography (PET) Radiopharmaceuticals in Saudi Arabia 3rd Gulf Nuclear Medicine, Kuwait, March 2009.
- I. Al Jammaz. Synthesis and *in vitro* and in vivo evaluation of Iodine-131-labeled folates: Potential molecular diagnostic and therapeutic radiopharmaceuticals. Radionuclides for Therapy Meeting, IAEA, Vienna, Austria, November 2009.
- I. Al Jammaz. National Needs and Plan for Radiopharmacy Training and Qualification, IAEA, Shanghai, China, July 2009.
- I. Al Jammaz. Developing a Post-graduate Course in Radiopharmacy Training. IAEA, Shanghai, China, July 2009.
- I. Al Jammaz. Production and Medical Applications of Radioisotopes, KFSHRC future scientist program, August 2009.

The Department of

GENETICS

Genetics

During 2009 the benefits of centrally supported program based research and service activities were again highlighted. Again work of the core and service facilities has increased substantially and acted in many instances to support and/or catalyze basic and translational research. It has been particularly satisfying to see this reflected in the number and impact of publications from the department during 2009 which included several that were institutionally recognized and awarded during the Research Centre's annual report. My congratulations are extended to the scientists, their collaborators and those who supported them in these achievements. Of particular note and an achievement of which we are all proud, is the recognition of Dr. Fowzan Alkuraya with the 2009 William K Bowes Jr award in Medical Genetics, recognizing excellence in research, teaching and clinical practice within the field. As is consistently the case, both the National Laboratory for Newborn Screening and the Molecular Diagnostic Laboratory have extended the level of clinical service they provide. During 2009 the department also continued build its technological expertise and capacity having introduced Next generation sequencing, molecular karyotyping, high throughput genotyping and expanded bioinformatics capabilities to deal with these. We look forward to the contribution of these initiatives during the year ahead.

CHAIRMAN

Brian Meyer, PhD

ADMINISTRATIVE STAFF

Lilia Fernandez
Klea M. Edquiban
Ralyn Alma O. Castillo

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

Nada Al Tassan, PhD

STAFF MEMBERS

Dania Khalil, BSc
Latifa Al Sharif, BSc
Jameela Shinwari, MSc
Manar Ghanam

RESEARCH PROJECTS

Project Title: Molecular Analysis of *APTX* and *SETX* genes in Saudi Families with Ataxia Ocular Apraxia (AOA).
RAC Project #: 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), one missense mutation was identified and analysis of this locus in ongoing.

Project Title: Genetic Mutations in Weill Marchesani Syndrome (WMS) in Saudi Arabia.
RAC Project #: 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. Two novel missense mutations in *ADAMTS10* were identified in two families. Linkage analysis on one family with 4 affected individuals with partial presentation of WMS symptoms revealed a disease locus in a 2.05-Mb region on 15q26.3, sequence of candidate genes identified *ADAMTS17* as novel gene causing a milder form of the disease (designated as WMS-like), three null mutations were identified in 6 patients from two families an in a single sporadic case. Further analysis and characterization of these genes in more patients is ongoing.

Project Title: Genetic Evaluation of Congenital Eyelid and Eye Movement Abnormalities.
RAC Project #: 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. A mosaic mutation .R954L was identified in two patients. 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. Sib-pair and linkage analysis is on going.

Project Title: Characterizing Genetic Abnormalities in Autistic Spectrum Disorder (ASD) patients in Saudi Arabia.
RAC Project #: 2080020
Investigators: *Al-Tassan N, Aldosari M, Nester M, Meyer B, Al Muslamani A, Bakheet D, Ayadhi L*

Project Description

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

Progress

Forty two families (multiplex and single) enrolled so far, Linkage analysis have revealed candidate loci on chromosome 7 in one family, sequencing of genes in this region is undergoing. Homozygosity mapping and sib-pair analysis in families with 2 affected individuals identified different disease loci on chromosome1,3,5,7,9,11,12,14 and 17. Genes in these loci are being further investigated.

Project Title: Genetic Characterization of Hemoglobinopathies in Saudi Arabia.
RAC Project #: 2080012
Investigators: *Bakheet D , Al Jafreri A, Warsy A, Al Anzi M, Al Tassan N*

Project Description

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

Progress

Seventy β- thalassaemia patients were enrolled from KKUH and KFSHRC. 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 Hyperinsulenimic Hypoglycemia of Infancy (Nesidioblastosis).
RAC Project #: 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 KFSH&RC screening for both genes identified a number of novel and reported variants. Deletions were also identified in some patients.

Project Title: The Molecular Basis of Inherited Reproductive Disorders.
RAC Project #: 209105
Investigators: *Al Tassan N, Meyer B, Alkuraya F, Wakil S, Monies D, Khalak H, Crowley W*

Project Description

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

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

1. Khan AO, Khalil DS, Al-Sharif LJ, AL-Ghadhfan FE, Al-Tassan NA. (2010) Germline Mosaicism for KIF21A Mutation (p.R954L) Mimicking Recessive Inheritance for Congenital Fibrosis of the Extraocular Muscles. *Opthalmology* 117(1):154-82.
2. Khan AO, Khalil DS, Al-Sharif LJ, Al-Tassan NA.(2009). Mutations in KIF21A and PHOX2A are absent in 16 patients with congenital vertical incomitant strabismus. *Ophthalmic Genet*. 30(4):206-7.
3. Morales J, Al-Sharif L, Khalil DS, Shinwari JM, Bavi P, Al-Mahrouqi RA, Al-Rajhi A, Alkuraya FS, Meyer BF, Al Tassan N (2009). Homozygous Mutations in ADAMTS10 and ADAMTS17 Cause Lenticular Myopia, Ectopia Lentis, Glaucoma, Spherophakia, and Short Stature. *Am J Hum Genet*. 85(5):558-6814.
4. Dallosso, A.R., Jones, S., Azzopardi, D., Moskvina, V., Al-Tassan, N., Williams, G.T., Idziaszczyk, S., Davies, D.R., Milewski, P., Williams, S., et al. (2009). The APC Variant p.Glu1317Gln Predisposes to Colorectal Adenomas by a Novel Mechanism of Relaxing the Target for Tumorigenic Somatic APC Mutations. *Hum Mutat*. 30(10):1412-8.
5. Oystreck DT, Khan AO, Vila-Coro AA, Oworu O, Al-Tassan N, Chan WM, Engle EC, Bosley TM.(2009) Synergistic divergence: a distinct ocular motility dysinnervation pattern. *Invest Ophthalmol Vis Sci*. 50(11):5213-6

Cardiovascular and Pharmacogenetics

RESEARCH PROJECTS

Project Title: Evaluation of the Relevance of Single Nucleotide Polymorphism for Coronary Artery Disease in the Saudi Population.
RAC Project #: 2010020
Investigators: *Nduna Dzimiri, Futwan Al-Mohanna, Maie Al-Shahid and Brian Meyer*

Project Description

This study aims at characterizing gene variants associated the risk of CAD in the Saudi population. In the first stage, we identify informative SNPs in the general population followed by the association assays in large populations.

Progress

During the report period, our efforts have been primarily directed at performing the association experiments in target populations of >4000 individuals. Thus far, we have collected data on several genes including the human endothelial transcription factors *GATA2* and *GATA4*, myocyte enhancer factor-2 (*MEF-2A*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*), paraoxonase 1 (*PON1*), proteasomal α-subunit type 6 (*PSMA6*), peroxisome proliferator-activated receptor α/β, (*PPAR*) and low density lipoprotein receptor (*LDLR*). The assays were run using TaqMan assays on real-time PCR system. Data is being analyzed to publication. Two manuscripts were published on this work during the report period.

HEAD OF UNIT

Nduna Dzimiri, PhD

STAFF MEMBERS

Paul Muiya
Samar El Hawari
Editha Andres
Mohammad Najai
Nejat Al Mazhar
Mary Grace Vigilla
Daisy Gueco

Project Title: Relevance of Lipid Metabolizing Proteins in the Treatment of Hypercholesterolemia and Coronary Heart Disease.
RAC Project #: 2030012
Investigators: *Nduna Dzimiri, Futwan Al-Mohanna, Maie Shahid and Brian Meyer*

Project Description

This study was designed to identify genes responsible for hyperlipidaemia and to test the role gene polymorphisms in variations in patient responses to antihypercholesterolemia therapy with statins (lipid lowering agents) in a target population of about 3,000 patients. We selected candidate genes from the cholesterol biosynthetic and lipid metobalic pathways including 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), cholesteryl ester transfer protein (CETP), 3-hydroxy-3-methylglutaryl-coenzyme A reductase, sterol regulatory element-binding protein subtype 2 (SREBP-2) and the SREBP cleavage-activating protein (SCAP).

Progress

During the current report period some familial studies using the whole genome scanning procedure idenfied a number of chromosomal loci possibly related to early onset of CAD in familial hyperlipidaemia (FH), heterozygous FH (HFH) and low high density lipoprortein disorders. Three familiar gene, low density lipoprotein receptor (LDLR), proprotein convertase subtilisin/kexin type 9 (PCSK9) and apolipoprotein B appeared to be consistently associated with early onset of CAD. Particularly noteworthy was the finding of strong association of a haplotype constructed from 11 LDLR variants with early onset of CAD, and a number of variants in both *LDLR* and PCSK9 that appear to be responsible for reduced HDL levels in individuals with dyslipidaemic disorders. These findings are being extended to the general population. Part of this data was published during the current report period. We also increased our population sizes for association of the various SREBP-2 and SCAP variants with response to simvastatin therapy. Data is currently being analyzed for publication.

Project Title: Clinical and Molecular Characterization of Patients With Inherited Arrhythmogenic Disorders.
RAC Project #: 2050035
Investigators: *Zohair Al-Hasnain, Nduna Dzimiri, Salma Majid, Majid Al-Fayyah, Yasssn Al Manea, Mohammed Al-Owain and Brian Meyer*

Project Description

This study focuses on identifying genes responsible for inherited arrhythmogenic disorders particularly the long QT syndrome (LQTS), Brugada and Sinus sick syndrome, in the Saudi population. This information should serve a number of clinical objectives including patient diagnosis, stratification and prophylactical strategies in the management of arrhythmogenic disorders.

Progress

More than families have been recruited thus far for the LQTS study. Preliminary linkage analysis points to novel loci as being associated with the syndrome. Further analysis to narrow down the region and identify some potential candidate genes is currently in progress. We also continue to recruit more families to enable us narrow down the interval and to identify more novel loci for this rare autosomal recessive disorder.

Cognitive Genetics

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

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

Though our unit is recently established, we have initiated several multidisciplinary research projects. 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

Namik Kaya, PhD

STAFF MEMBERS

Albandary Bin Bakheet MSc
Banan Al-Younes MSc

RESEARCH PROJECTS

Project Title: Genetic Basis of Mental Retardation in Families from KSA.
RAC Project #: 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 are collected. We have performed linkage analysis and homozygosity mapping on five families and narrowed down the linked regions using microsatellites. Targeted sequencing is ongoing for the selected genes.

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

Around six patient samples have been collected under the project and mutation analysis was done based on previous information. We are in the process of collecting more samples.

Project Title: Positional Cloning of Genes Underlying Genetic Disorders with Prominent Neurodevelopmental Manifestations in Several Extended Families.
RAC Project #: 2060 035
Investigators: Namik Kaya and 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, linkage and homozygosity mapping, targeted sequencing studies on the patients' samples.

Progress

DNA samples have been collected from consanguineous families (affected, unaffected, and parents). Previously collected samples were run on Affymetrix 10K and 250K SNP Mapping Assays. Genomic regions likely to harbor

disease causing mutations are under investigation by using fine mapping and targeted gene sequencing techniques. A manuscript is under preparation.

Project Title: Molecular Genetic Studies in Chromosome Disorders.
RAC Project #: 2040 042
Investigators: *Namik Kaya, Pinar Ozand, Nadia Sakati, Mehmet Inan, Dilek Colak, Fowzan Alkuraya, Ali Al-Odaib, Naji Al-Dosari, Claudia Walter*

Project Description

The specific aim of this project is to identify chromosomal abnormalities of patients clinically suspected to have a chromosome disorder 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 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: Pathogenesis of Early Infantile Primary Lactic Acidosis.
RAC Project #: 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. Two posters were presented at the Annual Research Day, KFSHRC 2008, and ASHG Meeting 2009; four manuscripts are under preparation.

Project Title: Hunting for One of the Autism Genes that Might be Linked to Osteopetrosis With Renal Tubular Acidosis.
RAC Project #: 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.

PUBLICATIONS

Recent Refereed Journal Research Articles

- Al-Owain M, Mohamed S, Kaya N, Zagal A, Matthijs G, Jaeken J.Al-Owain M, Mohamed S, Kaya N, Zagal A, Matthijs G, Jaeken J. A novel mutation and first report of dilated cardiomyopathy in ALG6-CDG (CDG-Ic): a case report. *Orphanet J Rare Dis*. 2010 Apr 16;5(1):7.
- Colak D, Kaya N, Al-Zahrani J, Al Bakheet A, Muiya P, Andres E, Quackenbush J, Dzimiri N. Left ventricular global transcriptional profiling in human end-stage dilated cardiomyopathy. *Genomics* 2009 Jul;94(1):20-31.
- 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 in 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.
- 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, Bouhoaigah 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 Aug 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

- N. Kaya, J. Al-Zahrani, N. Al-Dosari, D. Colak, T. Al-Sheddi, O. Al-Habit, B. Meyer, P. Ozand, N. Sakati. Molecular Characterization of a Chromosome 12q Telomeric Terminal Deletion in a Patient with Dysmorphia. Oct 2009, ASHG 59th Annual Meeting, Honolulu, HI, USA.

- M. Al-Owain, D. Colak, A. AlBakheet, B. AlYounes, A. Al-Aqeel, F. AlFadhli, A. Al-Hashem, A. Al-Odaib, M. Faiyaz-Ul-Haque, Z. Al-Hassnan, H. AL-Zeydan, Z. Al-Rahbeeni, M. Al-Sayed, S. AL-Alaiyan, K. Abu-Amero, P. Ozand, N. Kaya. Mutation analysis and genome-wide gene expression profiling on patients with primary lactic acidosis. Oct 2009, ASHG 59th Annual Meeting, Honolulu, HI, USA
- D. Colak, M. Chishti, A. AlBakheet, A. Al-Qahtani, M. Shoukri, M. Goyns, P. Ozand, J. Quackenbush, B. Park, N. Kaya. Integrative and comparative genomics analysis of early hepatocellular carcinoma differentiated from liver regeneration in young and old. Oct 2009, ASHG 59th Annual Meeting, Honolulu, HI, USA
- 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, HI, 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, 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.
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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 Ozand. 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

Computational Genetics

The Computational Genetics Section performs original and collaborative research 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.

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.
- Analytical processing of high throughput data (e.g.: gene expression, SNP genotyping, metabolic screening, DNA sequencing, metabolic screening).
- Identification of disease phentoype 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.

HEAD OF UNIT

Hanif Khalak

STAFF MEMBERS

Faris Abumelha
Recruitment for one additional engineer and one analyst in progress

RESEARCH PROJECTS

Summary List

- Establishment of a High-Performance Computing (HPC) Environment and Bioinformatics Portal for Research Genetics.
- RC Computing Network hardware and configuration performance upgrade.
- National Laboratory for Newborn Screening (NLNBS) LIMS and Web Infrastructure.
- Genomic Survey of Homozygosity and Copy Number Variations and Techniques for their Identification in a Consanguineous Population.
- Homozygosity Mapping of Saudi Colorectal Cancer Patients.
- Haplotype Analysis for Case-Control Association Studies (published and submitted articles).
- Bioinformatic Analysis of HCV, HCB, and H1N1 viral strains from Saudi isolates in the context of global epidemiological trends at a molecular level (manuscript submitted).

Project Title: Establishment of a High-Performance Computing (HPC) Environment and Bioinformatics Portal for Research Genetics.
Investigators: *H.G. Khalak, F. Abomelha, 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.

The computing capacity is being deployed to contribute to the establishment of mirror sites for critical genomic and genetic data, e.g. 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 have been in operation with <1% downtime and without data loss for high-performance computing capability. Scientific computing applications such as described above have been deployed, and used in a number of genomic (SNP, viral phylogenetics) and population (homozygosity, genotyping) studies. Individual core lab workflows have been and continue to be tested to migrate production tasks to adopt these workflows.

Project Title: RC Computing Network Hardware and Configuration Performance Upgrade.
Investigators: *F. Abomelha, H.G. Khalak, B.F. Meyer, W. Al-Goblan (ITA), S. Mohaisn (ITA)*

Project Description

The volume and throughput of data for projects within the Research Centre (RC) at KFSH&RC has grown quite substantially in the past few years, and this trend is increasing. Within the recent year, we have added several servers both in the RC's BESC server room as well as within racks in the ITA Data Centre, in order to process and manage this increasing research data stream. The access and transfer of data to and from these servers has in recent experience encountered significant latencies and transfer times. Addressing these issues will require systems and networking upgrades as well as re-configurations.

As per discussions with both the Server and Networking teams in Mr. Al-Madiny's group, we have identified a number of networking project tasks which will be of substantial value to the Research Centre's data management efforts.

Progress

Phase 1, upgrade/addition of 3 Cisco 2960 switches in the RC Basement and 2nd floor, for servers in BSSC and

Core labs is near completion and significantly improved network performance for RC servers. Subsequent plans are to migrate of all RC IP addresses onto a common, separate VLAN. In addition, upgrade has been completed by ITA of bandwidth for dedicated CCC Research intranet link to 20-30Mbit, and installation of new switch at CCC Research Department.

Phase II plans include upgrade of all switches to Cisco 3750, upgrade to 1Gbit cabling from network switches to BSSC and Core lab servers. In addition, procurement of additional 20-30Mbit internet bandwidth dedicated for RC servers and scientists, and a collaboration uplink between KFSH&RC and KAUST supercomputing facility.

Project Title: National Laboratory for Newborn Screening (NLNBS) LIMS and Web Infrastructure.
Investigators: *H.G. Khalak, A. Al-Odaib, F. Badoui, S. Al-Ageel (BESC), P. Siddiqui (BESC), A.R. Al-Thuwaini (PSCDR)*

Project Description

The Newborn Screening (NBS) 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, recovery, robustness and access at a number of levels:

1. *Hardware:* lab computer systems (SpecimenGate LIMS) → clustered severs
2. *Network:* cables and switches (Ethernet and Fiber Optic) → redundancy
3. *Data:* disk and database level-mirroring → redundancy and backups
4. *Access:* web site portal for NBS related information and data reporting

Working with system vendors (Perkin-Elmer, HVD Systems), ITA, and BESC Computer Support, the NBS team's goal was to deploy a robust, reliable, and high-performance solution to meet the requirements of the NBS program, institutional clients and patients, PSCDR, and Ministry of Health.

Progress

From March 2009, the NBS LIMS (SpecimenGate) was deployed by PE/HVD and operational tests were not found to meet minimum NBS requirements due to failure of network connectivity from power failures. Working with the vendors, new configurations and Standard Operating Procedures (SOPs) were established with respect to operation, maintenance, and recovery of the LIMS systems and applications in accordance with the NBS requirements. In addition, a NLNBS web site was developed providing access to Newborn Screening concepts, program, and services, to the public as well as data statistics and reports to client institutions. Currently, requirements have been specified for a major redesign of the web site, in order to accommodate mobility and remote-access requirements, and easier access to specific NBS information and data.

Project Title: Genomic Survey of Homozygosity and Copy Number Variations and Techniques for their Identification in a Consanguineous Population.
Investigators: *H.G. Khalak, F. Al-Kuraya, A. Al-Azami, B.W. Meyer*

Project Description

The genetic component of human disease consists primarily of mutations and variation in copy number of DNA in the genome. Methods mapping regions of homozygosity and CNV (copy-number variation) are yielding significant findings contributing to the identification of novel genes and variants associated with disease. The aim is to leverage the enrichment of features in the DNA of consanguineous families already studied in rare diseases to help catalog "normal" and "aberrant" variants to better understand the role of these DNA regions with respect to disease and embryogenesis.

Progress

We have collated and analyzed results from studies of many consented families from existing research programs

in vision impairment, neurogenetics, metabolic diseases, and hereditary deafness. We used a number of available and custom tools (Genotyping Console CNAG, Partek, R/BioConductor) on our high-performance computing (HPC) system to analyze existing genome SNP data from ~1000 individuals. One paper related to CNVs was submitted to Science and two papers related to homozygosity mapping to find disease genes are in preparation.

Project Title: Homozygosity Mapping of Saudi Colorectal Cancer Patients.
Investigators: *H.G. Khalak, K. Siraj, K. Al-Kuraya, F. Al-Kuraya*

Project Description

In order to identify genetic variations which confer susceptibility to colorectal cancer (CRC) would generally require the genotyping of a prohibitively large sample of patients. Methods to map regions of homozygosity are able to identify significant recessively acting mutations contributing to the onset of disease, particularly in outbred populations. Previous studies have produced conflicting results, but more recently have not found evidence to link regions of homozygosity to CRC. This study investigates this issue in the Saudi population.

Progress

Analysis of ~50 CRC samples versus 100 normal controls yielded a number of regions of homozygosity which were significantly higher proportion in CRC; genes within these regions are being investigated for mutations. No significant association was found for total number or length of these regions between CRC and normal samples. A paper (Siraj et al) is in preparation.

Project Title: Haplotype Analysis for Case-Control Association Studies.
Investigators: *H.G. Khalak, N. Dzimiri*

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), myocardial infarction (MI), hyperlipidemima (HL), hypertension (HT), and diabetes milletus (DM) within Saudi patients.

Progress

Analyses of association at the level of allele, genotype, and haplotype have been conducted on patient data for markers within loci for a number of genes (including PSMA6, MEF2A, GATA4, PON1). Successful application of modules within the SAS, SPSS, and R software packages has contributed to articles submitted for publication, including the identification of haplotypes associated with a common between the various cardiovascular and metabolic phenotypes (CAD, MI, HL, HT, DM).

Project Title: Bioinformatic Analysis of HCV, HBV, H1N1, and H5N1 Viral Strains from Saudi Isolates in the Context of Global Epidemiological Trends at a Molecular Level.
Investigators: *H.G. Khalak, A. Al-Qahtani (BMR), A. Al-Ahdal (BMR)*

Project Description

Prevalence and impact of infectious disease agents, particularly viruses, is becoming of increasing clinical and research importance. This work involves the investigation and application of bioinformatics techniques and tools to model and analyze DNA and protein sequences derived from Saudi viral strains within relevant host (animal and human) populations. Application of bioinformatics in this regards ranges from QC and assembly of DNA fragments into contigs (ChromasPro, SeqMan), to multiple sequenct alignment and phylogenetic analysis of viral strains (MegaAlign, ClustalW, Dendroscope, HMMer), to sequence/structure comparison (SNPs3D, HCVdb) to identify important SNPs and clades within populations.

Progress

Bioinformatics techniques and tools described above have been and continue to be applied to sequence generated in the BMR Virology and Infectious Disease Unit. We have demonstrated the utility of these tools to discover clusters of strains within the Saudi isolates, and identify and confirm important sites in viral proteins. We are in the process of performing followup studies including further bioinformatic analyses at the DNA and protein level.

PUBLICATIONS

Refereed Journal Research Articles

- Khalak, HG, Ahmad F, Wakil SM, Abu Safieh L, Aldahmesh M, Al-Dosari M, Monies D, Kaya N, Al-Hamed M, Alzahrani F, Al-Jbali L, Al-Tassan N, Shamseldin H, Shaheen R, Al-Rashed M, Baz B, Hagos S, Abu-Dhaim N, Meyer BW, Alazami AM, Alkuraya FS. Genic and Nongenic Human DNA is biased against Nullizygosity. *Science*, submitted.
- Aldahmesh MA, Abu Safieh L, Alkuraya H, Al-Rajhi A, Shamseldin H, Hashem M, Alzahrani F, Khan AO, Alqahtani F, Rahbeeni Z, Alowain M, Khalak H, Al-Hazzaa S, Meyer BF, Alkuraya FS. Molecular characterization of retinitis pigmentosa in Saudi Arabia. *Mol Vis*. 2009 Nov 24;15:2464-9.
- Elhawari S, Al-Boudari O, Muiya P, Khalak H, Andres E, Al-Shahid M, Al-Dosari M, Meyer BF, Al-Mohanna F, Dzimiri N. A study of the role of the myocyte-specific enhancer factor-2A gene in coronary artery disease. *Atherosclerosis*. 2009 Sep 9.

Local Conferences and Meetings

- Attended Inaugural Symposium for KSU Center of Excellence for Biotechnology, March 2009.
- Presented Inaugural lecture on DNA Bioinformatics for KSU DNA Chair Lecture Series, March 2009.

Training Courses Taught

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
05/2009	Medical Genetics Grand Rounds Lecture on Computational Genetics
17-19/04/2010	Introduction to Bioinformatics (10 CME credits), 55+ registered and paid students

Developmental Genetics

The research focus of our section is the study of normal human morphogenesis by studying the genetics of human malformation syndromes. In particular, we are interested in single gene defects that result in craniofacial and eye developmental anomalies. We use the latest genomic tools to identify these genes and then apply standard developmental biology assays to establish their role in development. Clearly, this work is extremely important academically as it represents important contribution to the functional annotation of the human genome, a daunting but necessary task if we are to unlock the mysteries of the human genome and how it controls normal human embryogenesis. However, no less important is the potential of our research to identify the causative genetic defect in the families afflicted with these Mendelian forms of developmental anomalies which is a pre-requisite to the implementation of preventive genetic services which we see as a direct translational benefit of our work.

HEAD OF UNIT

Fowzan Alkuraya, MD

STAFF MEMBERS

Anas Alazami, DPhil
Mohamed Aldahmesh, PhD
Leen Abu Safieh, PhD
Ranad Shaheen, PhD
Hanan Shamsheldin
Lama Al-Abdi
Fatma Al-Zahrani
Mais Hashem
Jawahir Yousuf Nur

RESEARCH PROJECTS

The two major projects in our section are:

1. Genetics of Vision Loss in Saudi Arabia: This is a KACST-funded project that aims at deciphering the genetic causes of vision impairment, particularly those that can be attributed to pure developmental aberration e.g. anterior segment dysgenesis, congenital cataract, etc. In the course of this work, the identified genes are developmentally annotated.

2. Genetics of Craniofacial Birth Defects in Saudi Arabia: This is a DHFMR-funded project whose aim is to study genetic mutations that lead to craniofacial anomalies. Eventually, it may be possible to predict with great precision what the craniofacial phenotype is based on the genotype and this will have great forensic applications.

PUBLICATIONS

- Alkuraya FS, Kilani RA. Attitude of Saudi families affected with hemoglobinopathies towards prenatal screening and abortion and the influence of religious ruling (Fatwa). *Prenat Diagn*. 2001 Jun;21(6):448-51. PubMed PMID: 11438947.
- Alkuraya FS. Index of suspicion. Pediatr Rev. 2004 Aug;25(8):289-94. *PubMed PMID*: 15286275.
- Alkuraya FS, Harris DJ. Trisomy 8 mosaicism in a patient with heterotaxia. Birth Defects Res A Clin Mol Teratol. 2005 Jan;73(1):58-60. *PubMed PMID*: 15578648.
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- Higgins AW, Alkuraya FS, Bosco AF, Brown KK, Bruns GA, Donovan DJ, Eisenman R, Fan Y, Farra CG, Ferguson HL, Gusella JF, Harris DJ, Herrick SR, Kelly C, Kim HG, Kishikawa S, Korf BR, Kulkarni S, Lally E, Leach NT, Lemyre E, Lewis J, Ligon AH, Lu W, Maas RL, MacDonald ME, Moore SD, Peters RE, Quade BJ, Quintero-Rivera F, Saadi I, Shen Y, Shendure J, Williamson RE, Morton CC. Characterization of apparently balanced chromosomal rearrangements from the developmental genome anatomy project. *Am J Hum Genet*. 2008 Mar;82(3):712-22. *PubMed PMID*: 18319076; *PubMed Central PMCID*: PMC2427206.
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First Arabian Hereditary Deafness (FAHD) Unit

OVERVIEW:

1. To identify known and novel genes causing hereditary hearing loss in the Saudi Arabian population.
2. To provide a primary platform for the design, validation and implementation of molecular diagnostic testing for inherited diseases to help lay the foundation for preventative measures including carrier testing, prenatal diagnosis, pre-implantation genetic diagnosis and pre-marital screening.

HEAD OF UNIT

Faiqa Imtiaz Ahmad, PhD

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Khushnooda Ramzan, PhD
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Bashayer Al-Mubarak *(PhD Student)*
Rabab Allam
Abeer Al Mostafa
Mosaab Doubi
Lolowa Jomaa

RESEARCH PROJECTS

Project Title: Molecular Characterization of Hereditary Deafness in Saudi Population.
RAC Project #: 2100 001
(KACST#08-MED495-20: RAC# 2100 001)
Investigators: *Faiqa Imtiaz, PhD, Mohammad Al-Owain, MD, Khushnooda Ramzan, Phd, Selwa AF Al-Hazzaa, MD, Ms Ghada Bin-Khamis, Ahood Sulaiman, MSc*

Project Description

Recessively inherited diseases are more prevalent in populations where consanguineous marriages are common, like Saudi Arabia. Deafness is the most common sensory deficit in humans (1:1000 child births) with both genetic (50%) and environmental (50%) etiologies. Our study hopes to define the genetics of deafness in this population. Families with profound congenital deafness and an autosomal recessive mode of inheritance are a powerful resource for genetic linkage studies of recessively inherited deafness.

Progress

1. 2-year project to study hereditary deafness awarded and funded by KACST in 2009.
2. 3 year fellowship awarded to Dr. Faiqa Imtiaz from the Dubai Harvard Foundation, between KFSH&RC and the laboratory of Professor Cynthia Morton at Harvard Medical School for the investigation of the genetic causes of hereditary deafness in Saudi Arabia.
3. Successfully completed 3-year PSCDR funded project to study “Role of DFNB1 in the Saudi Population”.

Gene Therapy Unit

Gene Therapy Unit is currently conducting experimental gene therapy research on thyroid cancer, elucidating molecular defects leading to thyroid tumorigenesis, and molecular genetic analysis of genes involved in endocrine disorders. Significant progress has been made on each front. We demonstrated that IL-12 could induce succinate receptor expression, which in turn down-regulate HIF-1 expression, causing apoptosis of thyroid cancer cells. 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 large Saudi family with papillary thyroid carcinoma arising from congenital goiter. We demonstrated that biallelic c.6725G>A (p.R2223H) mutation causes Tg retention in the ER, resulting in dyshormonogenesis. Prolonged TSH stimulation may promote malignant transformation and development of thyroid cancer.

HEAD OF UNIT

Yufei Shi

STAFF MEMBERS

Minjing Zou
Essa Baitei
Roua Al-Rijjal

RESEARCH PROJECTS

Project Title: IL-12 Gene Therapy of Anaplastic Thyroid Carcinoma.
RAC Project #: 2030057
Investigators: *Yufei Shi, Ali Al-zahrani, Ranjit S. Parhar, Minjing Zou*

Project Description

The incidence of thyroid cancer in Saudi Arabia is higher than that in the US. Based on the Cancer Incidence Report 1997-1998, National Cancer Registry, Ministry of Health, Kingdom of Saudi Arabia, the five most common cancers among 5231 female Saudi patients are breast (19.8%), thyroid (9.5%), leukemia (6.3%), NHL (6.1), and ovary (4.5%). In the US, however, the incidence of thyroid cancer is only 2% and is the eighth of the most common cancers (Cancer facts and figures 2002, American Cancer Society). Anaplastic thyroid carcinoma is the most aggressive type of thyroid malignancies with a mean survival time of less than 8 months. No effective therapeutic approach is currently available, making the development of novel treatments necessary. Interleukin 12 (IL-12) is a proinflammatory heterodimeric cytokine with strong antitumor activity. In the present study, we investigated the potential of IL-12 gene therapy for anaplastic thyroid carcinoma in BALB/c (*nu/nu*) nude mice.

Progress

Previously, we demonstrated that tumorigenicity of anaplastic thyroid carcinoma cell line ARO was significantly reduced following interleukin 12 (IL-12) gene transfer in nude mice. We suspected that tumor target structure in ARO/IL-12 cells might be changed as a result of IL-12 expression and such a change may make them more susceptible to be killed through mechanisms apart from NK-dependent pathway (Human Gene Therapy, 14, 1741, 2003). To identify genes involved in the change of tumor target structure in ARO/IL-12 cells, we examined gene expression profile of ARO and ARO/IL-12 by microarray analysis. We found that succinate receptor is highly expressed in ARO/IL-12 cells than ARO cells. It has been reported that triggering the succinate receptor GPR91 on dendritic cells enhances immunity. Overexpression of GPR91 in ARO and Hek 293 cells can down-regulate HIF-1 expression and cause apoptosis. These data suggest that GPR91 plays a role in IL-12 mediated tumor regression.

Project Title: Investigation of BRAF Mutation in Thyroid Carcinoma from Saudi Population.
RAC Project #: 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 V^{600E} 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-PCT 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: Investigation of Genetic Defects Causing Follicular Variant of Papillary Thyroid Cancer Arising from Congenital Goiter in a Large Family.
RAC Project #: 2090023
Investigators: *Hussein Raef, and Yufei Shi*

Project Description

Dyshormonogenesis due to genetic defect in thyroglobulin (Tg) synthesis and secretion can lead to congenital hypothyroidism and the development of large multinodular goiters especially in those not adequately replaced with L-thyroxin. Thyroid carcinoma has also been reported to develop in such cases. Here we report two sisters (ages 25 and 31) with congenital hypothyroidism, who went on to develop large multinodular goiters. Serum Tg was undetectable. They had sub-total thyroidectomies done at age 12 and 21 years, respectively, with multinodular goiter histology, but with the presence of micro-foci of follicular variant of papillary thyroid cancer (FVPTC) in the older sister only. They both developed recurrence of thyroid nodules, but only the older subject who was frequently non compliant with L-Thyroxin replacement-progressed to develop iodine avid FVPTC in the cervical region and later as regional and distant (lung and bone) metastasis. The underlying molecular defects were investigated.

Progress

The entire coding region of *TG* gene was sequenced. *BRAF*, *RAS*, and *P53* mutations or *PAX8/PPAR-γ* rearrangement were screened from FVPTC tumor. Tg expression was studied by immunohistochemistry. Biallelic c.6725G>A (p.R2223H) and c.6396C>T (p.S2113L) sequence variations were detected in both patients and monoallelic variations in their family members. The c.6396C>T (p.S2113L) sequence variation was found in 14% of 100 population controls whereas c.6725G>A variation was not present in the controls. Strong cytoplasmic immunostaining of Tg was observed in the hyperplastic thyroid epithelial cells and weak or no staining in the follicular lumen. Cytoplasmic staining was localized in the endoplasmic reticulum (ER). Reduced staining was found in the FVPTC. Neither *RAS*, *BRAF*, or *P53* gene mutation nor *PAX8/PPAR-γ* rearrangement was detected in the tumor tissue. These data suggest that biallelic c.6725G>A (p.R2223H) mutation causes Tg retention in the ER, resulting in dyshormonogenesis. Prolonged TSH stimulation may promote malignant transformation and development of thyroid cancer. The c.6396C>T (p.S2113L) is a novel polymorphism.

PUBLICATIONS

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- Biallelic p.R2223H Mutation in the Thyroglobulin Gene Causes Thyroglobulin Retention and Severe Hypothyroidism with Subsequent Development of Thyroid Carcinoma. Raef H, Al-Rijjal RA, Al-shehri S, Zou MJ, Al-Mana H, Baitei EY, Parhar RS, Al-Mohanna FA, and Shi Y. *J Clin Endocrinol Metab*. 95:1000-1006, 2010.

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 GeneChip Stations, the core facility genotypes thousands of samples Human Mapping Genchip arrays for 250K, and for SNP 6.0 which includes 1 million SNPs and 400k non-polymorphic probes for copy number variation analysis/ LOH on a single array. For the RNA profiling, large number of samples are processed for U133 Gene expression array and Human ST 1.0 arrays to study the differential gene expression. The laboratory is now equipped to do high through put with the help of Axiom Gene Titan which will allow to do Genome Wide Association Studies for various disorders.

Besides a large of research projects involving mapping studies are undertaken at the unit.

HEAD OF UNIT

Salma Wakil, PhD

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RESEARCH PROJECTS

Project Title: Mapping of X-linked Diseases With Mitochondrial Abnormalities.
RAC Project #: 2060 018

Project Description

In this project whole genome scanning was done using affymetrix 250styl 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 Arrhymogenic Disorders.
RAC Project #: 2050 035

Project Description

This project is in collaboration with pharmacogenetics unit where the candidate 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 Rhematoid Arthritis.
RAC Project #: 2020 023)

Project Description

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

Project Title: Identifying the Chromosomal Location of the Gene Underlying a Novel Autosomal Recessive Syndrome of Myopathy.
RAC Project #: 2020 008

Project Description

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.

Project Title: Molecular Characterisation of Hereditary Spastic Paraplegia.
RAC Project #: 2090 011

Project Description

In this project we aim to idenitify the known and unknown variations in various genes and with functional studies, able to characterize and understand the disease mechanism of HSP in this population.

Hereditary Immunology

The immunology section has been focused on investigating the underlying molecular defects of many of the primary immunodeficiency diseases (PID) in Saudi Arabia patient population. Off the 100 inherited PIDs, we are focusing our attention to Severe Combined Immunodeficiency Diseases, Chronic Granulomatous Disease (CGD), Familial Hemophagocytotic Lymphohistocytosis (FHL), Hyper-IgM Syndromes, Agammaglobulinaemia (Bruton's Disease), MHC class II deficiency (Bare lymphocytes), X-Linked Lymphoproliferative Syndrome (XLP), Immunodysregulation Polyendocrinopathy and Enteropathy (IPEX), Autoimmune Lymphoproliferative Syndrome (ALPS), Leukocyte Adhesion Deficiency (LAD1), Griscelli Syndrom, Wiskott-Aldrich Syndrome, Chediak-Higashi Syndrome, Ataxia-telangiectasia, and Hyper IgE Syndrome. PIDs results from genetic defects in gene responsible for the development or function of T-, B-, NK-, phagocytic cells or the complement system. The incidence of the aforementioned diseases is higher in Saudi population than any other country due to the high rate of consanguinity. Many of the genes responsible for most of the international PID cases have been identified. However, we have a pool of Saudi patients the tested negative for all of the known genes. The challenge is to identify the genetic causes of these negative cases that are unique to the Saudi population. We will employ homozygocity studies using microarray gene chip technology for this purpose.

HEAD OF UNIT

Abbas Hawwari, PhD

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RESEARCH PROJECTS

Project Title: Underlying Molecular Genetic Defects of Primary Immunodeficiency Diseases In Saudi Arabia.
RAC Project #: 2080 025
Investigators: *Abbas Hawwari, PhD, Hamoud Al-Mousa, ABP, SBP, Abdulaziz Al-Ghonaium, Hasan Al-Dhekri, Saleh Al-Muhsen, Bandar Al-Saud, Rand Arnaout, Dorota Monies, Mohamed Al-Hamed*

Project Description

There are wide varieties of primary immunodeficiency diseases (PIDs) that are caused by congenital defects of the immune system. Today, over 100 inherited PIDs are known to exist, with an incidence estimate of 1 in 10,000 to 1 in 2000 among live births. These include X-linked agammaglobulinemia (Bruton's Disease), common variable immune deficiency (CVID), selective IgA deficiency, and severe combined immune deficiency (SCID). PIDs result from defects in T-, B-, NK-, phagocytic cells or the complement system. Certain PID types like CVID and selective IgA deficiency are not always familial; their cause is unknown but the interaction of genetic and environmental factors may play a role in their causation. If untreated, PIDs may associate with frequent life-threatening infections and debilitating illnesses. The genes responsible for most of these diseases have been identified due to modern advances in molecular diagnostics, which enabled early disease detection and adequate treatment. Mutation detection approaches are available to identify mutations through genotyping and direct sequencing. As would be expected, the incidence of these disorders in Saudi Arabia is higher than the world overall rates due to high consanguinity, and there is a need to delineate the molecular bases underlying them. Based on our experience with the RAC-approved SCID project, it is anticipated that novel gene mutations and novel loci/genes that are unique to the Saudi population will be discovered. Results roots out from these studies will benefit patients and their families in terms of counseling, disease prevention through pre-implantation genetic diagnosis and prenatal diagnosis.

Project Title: Underlying Molecular Defects of Chronic Granulomatous Disease In a Cohort of Saudi Patients.
RAC Project #: 2070 017
Investigators: *Abbas Hawwari, PhD, Saleh Al-Muhsen, MD, FRCPC, FAAP, Abdulaziz Al-Ghonaium, Hmoud Al-Mousa, Hasan Al-Dhekry, Sulaiman Al-Gazlan, Hasan Al-Rayes, Rand Arnaout, Anas Al Azami*

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 worldwide.

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 P67phox respectively.[5-10] Recent data from a large national US registry indicated the XL-recessive form tend to present earlier and follow more severe course.

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.

Project Title: Underlying Genetics of Familial Hemophagocytic Lymphohistiocytosis (FHL) In Saudi Arabia.

RAC Project #: 2080 041

Investigators: *Abbas Hawwari, PhD, Ali Al-Ahmari, MD, Bandar Al Saud, MD, Ibrahim Al-Fawaz, MD, Mohab Ayas MD*

Project Description

Hemphagocytic lymphohistiocytosis (HLH) is a life threatening condition characterized by hyperinflammation on the basis of various inherited or acquired immunodeficiency. A constant laboratory finding is impaired or absent fuction of natural killer (NK) cells and cytotoxic T cells (CTL). Familial Hemophagocytic Lymphohistiocytosis (FHL) is an autosomal recessive condition in which several genetic defects have been revealed. Studies in recent years have served to unravel the underlying genetic defects in some, but not all forms of FHL. These findings have provided an explanation for the defective cytotoxic cell function in FHL. These findings may also facilitate genetic counseling and prenatal diagnosis in affected families. Molecular defects of Saudi patients with FHL are unknown. This study is going to elucidate the genetic defects in this subgroup of patients.

National Laboratory for Newborn Screening

The National Laboratory for Newborn Screening (NLNBS) is both a service and research unit and is currently in contract with Prince Salman Center for Disability Research (PSCDR) to execute the Saudi Newborn Screening Program. The number of participating hospitals is presently thirty (30) in 2009. As a result, the number of screened newborns by the program increased to approximately one hundred thirteen thousand (113,000). In addition to the newborn screening, the NLNBS conducted about six hundred fifteen thousand (615,000) 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.

HEAD OF UNIT

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THE NATIONAL NEWBORN SCREENING

The National Newborn screening is a public health program implemented to detect and prevent selected congenital and heritable disorders. These disorders cause severe mental retardation, illness, or death if not treated early in life. Numerous studies showed that early detection and early intervention may prevent these consequences.

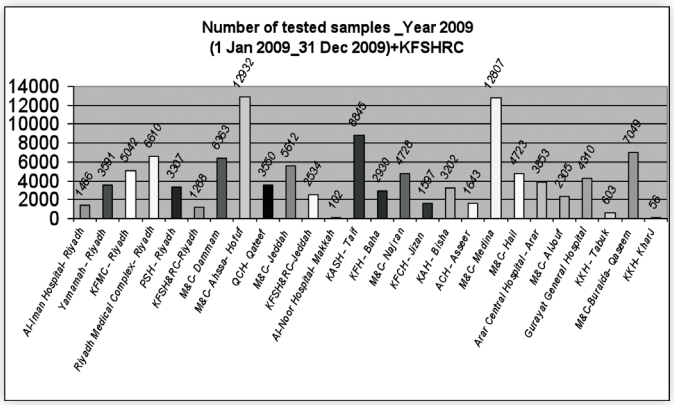
The program targets three hundred thousand (300,000) newborns from two hundred forty (240) birth center in different regions of KSA. The program includes screening dried blood spots from newborns at 24-72 hours after birth for sixteen (16) inherited metabolic and endocrine disorders (see list below).

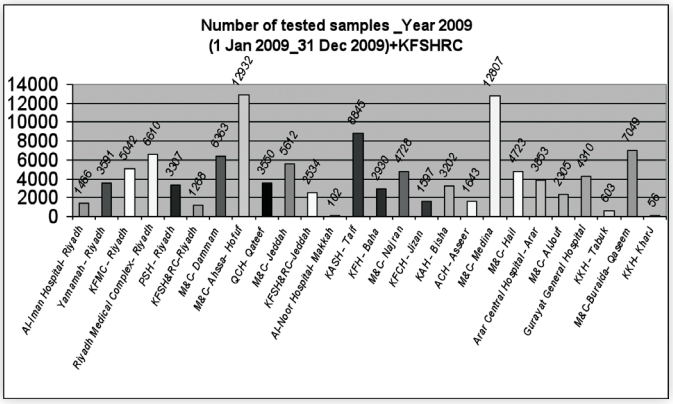
1. Phenylketonuria (PKU)
2. Maple Syrup Urine Disease (MSUD)
3. Arginosuccinase Deficiency (ASL)
4. Citrullinemia (ASD)
5. HMG-CoA Lyase Deficiency (HMG)
6. Isovaleric Acidemia (IVA)
7. Methylmalonic Acidemia (MMA)
8. Propionic Acidemia (PA)
9. Beta-ketothiolase Deficiency (BKT)
10. Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)
11. Glutaric Acidemia type-I (GA-I)
12. Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
13. Galactosemia (GAL)
14. Congenital Hypothyroidism (CH)
15. Congenital adrenal Hyperplasia (CAH)
16. Biotinidase Deficiency (BD)

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

In 2009, the Ministry of Health assigned Prince Salman Center for Disability Research (PSCDR) to execute the National Newborn Screening for 300,000 newborns. 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. During 2009, NLNBS managed to screen more than hundred thirteen thousand (113,000 babies) and fifty thousand specialized diagnostic assays. In total, the Laboratory performed more than six hundred fifteen thousand (615,000) different tests in 2009. Eighty eight (88) babies were found to be affected yield to a total of 395 affected newborn were detected since the start of the program. The incidence for the 16 screened diseases was 1:925. We are currently working closely with the Ministry of Health to execute the expansion of the program to cover the screening of three hundred thousand (300,000) newborns in 2010-2011.





RESEARCH PROJECTS

In addition to the clinical services, NLNBS conducts several research projects and validate several assays including screening Tyrosinemia type I. Moreover, the NLNBS in collaboration with international institutes provides the extremely specialized diagnostic service of complementation analysis for peroxisomal diseases and we are in the process to import the know-how into KFSHRC in the near future.

Project Title: Chemical Derivatization Approach to Improve the Mass Spectrometric Characteristics of Biological Markers and its Application for the Diagnosis of 3-Methylglutaconic-Acidurias.
Investigator: *Ali Al-Odaib, PhD*

Project Description

Investigating a new derivatization approach that involves the use of 4-[2-(N,N-dimethylamino)ethylaminosulfonyl]-7-(2-aminoethylamino)-2,1,3-benzoxadiazole (DAABD-AE) for the analysis of a selected group of closely related and clinically important dicarboxylic acids in 3MGCA. This reagent contains several ionizable sites with high proton affinity to improve the electrospray ionization (ESI) process and a hydrophobic benzofurazan moiety anticipated to improve the chromatographic behavior and retention of the derivative. To improve the turnaround time for the assays, we will combine this approach with the use of the relatively recent technology of ultra-performance liquid chromatography (UPLC).

Project Title: Replication for Genetic Association Studies on Birth Weight and Gestational Age.
RAC Project #: 2100 007)
Investigators: *Brian Meyer, PhD, Fowzan AlKuraya, PhD, Ali Al-Odaib, PhD, Dorota Monies, PhD*

Project Description

To examine genetic associations that can be found in Saudi newborns for birth weight and gestational time. We are studying differences of minor allele frequency compared to Caucasians and any effect this may have on birth weight.

Project Title: Congenital Hypothyroidism in Saudi Arabia: Molecular Characterization of Underlying Genetic Defects Causing Thyroid Dyshormonogenesis and a Long-term Follow-up.

Project Description

In this project we plan to follow up100-200 cases of previously diagnosed CH to characterize their underlying genetic defects and to determine what percentage of these cases that still have clinical or subclinical hypothyroidism. The project will provide insight and valuable feedback information on the success of CH newborn screening program in the Kingdom, and lay the molecular bases of genetic counseling for these patients and their family members to prevent inheritance of the disease in their offspring.

Project Title: Relationships between Serum Resistin and Leptin Levels, Body Mass Index, Lipid Profile, Polymorphisms in the Resistin Gene Promoter and Leptin Receptor Gene in Obese Saudi Children.
RAC Project #: 2050 030
Investigators: *Dr. Maha Daghestani, Dr. Ali Al-Odaib, Dr. Pinar Ozand, Dr. Namik Kaya*

Project Description

Children obesity is a complex trait influenced by interacting environmental hormonal and genetic factors. Resistin is a novel adipocyte-secreted hormone that has been proposed to be the link between obesity and diabetes, although little appears to be known regarding the physiological role of resistin in human. We are exploring the relationship between serum levels of resistin and leptin and certain anthropometric and metabolic parameters, and evaluate the associations between body composition variables and three common leptin receptor gene polymorphisms (K109R, Q223R, and K656N) and C/G SNP in promoter of RETN gene.

OTHER PROJECTS

Characterization of Peroxisomal Biogenesis Disorders Saudi Arabia, Clinical, Biochemical, and Molecular Studies

Evaluating Knowledge, Attitudes and the Psychosocial Impact of Newborn Screening in the Saudi Population (RAC# 2081 081).

Saudi Diagnostics Laboratory

In 2009 Saudi Diagnostic Laboratories (SDL) used the translational Research Programs of the Department of Genetics for the provision of molecular diagnostic services for patient care. The laboratory is fully accredited by the College of American Pathologists. SDL continues to be characterized by its focus on the molecular basis of a large number of Mendelian diseases and continues to identify Arab specific mutations for these disorders. As a consequence the repertoire of genes/mutations for which clinical diagnostic services are offered has increased substantially during 2009.

SDL now performs a repertoire of over 150 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. During 2009 in excess of 250 requests for molecular karyotyping were processed and this continues to be a growth area. Animal genetics was a significant component of services offered by SDL. Once again it has processed over 1000 samples for parentage verification of Arabian horses and participates in the International program for proficiency testing in this field. In addition SDL initiated the testing of camel samples also for parentage verification.

SDL provides diagnostic services for many clinical departments and sections at KFSHRC. These include Medical Genetics, Pediatrics, Neurosciences, Obstetrics and Gynecology, Pediatric Immunology and Pediatric Nephrology among others. During 2009 over 2000 diagnostic tests were performed by SDL in support of these services.

Preventative medicine through carrier detection, pre-implantation genetic diagnosis and prenatal testing is a major service activity of SDL. Prenatal testing is a regular part of the SDL workflow with almost 100 cases having been processed in 2009. SDL expanded its repertoire of testing and customer base throughout the kingdom in 2009.

HEAD OF UNIT

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STAFF MEMBERS

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Mohammed Al Hamed, MSc
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Amal Jaafar
Rula Abouthuraya
Sara Al-Haibey

Sequencing Core Facility

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

HEAD OF UNIT

Dorota Monies, PhD

STAFF MEMBERS

Mohamed Rajab, BSc *(MSR)*
Shamsa Al-Enazi, BSc *(Grant)*
Syeda Mashael Zaidi MSc *(Grant)*

SERVICES OFFERED

DNA Purification

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

DNA Sequencing

All DNA samples are sequenced using BigDye Terminator chemistry with universal M13 forward and reverse primers or user-supplied primers .The DNA sequencing reactions are electrophoresed on ABI's 3730xl DNA Analyzers which can produce read lengths of 1000 bases for high quality DNA templates. All sequencing reaction plates and individual samples have acceptable quality controls before the results are released. The DNA Sequencing Facility employs both objective and subjective quality controls. All samples have to be submitted to the laboratory according to the Sequencing Core Facility Requirements (see attachment below).

Objective Quality Controls

The facility places 2 controls on each sequencing plate. The controls consist of one negative and one positive controls. The negative controls consist of water being added to the sequencing reaction instead of DNA template. This control detects proper sequencing reaction plate setup, purity of the water used in the sequencing reactions, and any cross-contamination between the 96 wells of the reaction plate. The positive controls consist of M13 primers being used to sequence pGEM 3Zf(+).

For each sequencing reaction plate, all negative controls must be negative and the positive controls must pass certain quality criteria before sequences are released to each investigator.

Subjective Quality Controls

All sequences are reviewed by trained staff in the DNA Sequencing Facility. A sequence reaction is considered successful if the sequence contains high quality base calls for at least 90% of the first 700 bases. If the sequence fulfills the above criteria and the negative/positive plate controls pass the set quality criteria, the sequence is released to the investigator. If a sequence fails the subjective quality control, the sequence is investigated with troubleshooting and "redo" policy.

ADDITIONAL SERVICES

Fragment analysis

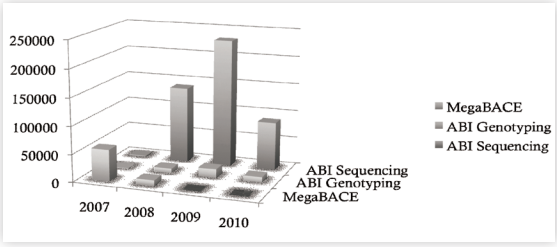
The DNA Sequencing Facility also provides a DNA fragment analysis service. The fragment analysis service is used for microsatellite genotyping, SNP genotyping and mutation detection. The DNA Sequencing Facility performs high throughput analysis of microsatellite markers using the Applied Biosystems 3730xl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

Oligo orders

We cooperate with *Metabion International AG* from Germany which offers a complete spectrum of custom oligos - from high quality/high throughput oligos (MTP formats) to high-quality special oligos like Real-time PCR probes including LightCycler® probes.Custom DNA Primers and Probes are available as standard deoxynucleotides, modified bases, 5' modified nucleotides, S-oligos for antisense studies. They are available in different scales: 3 standard scales for dual labelled fluorogenic probes, some single labelled DNA-oligonucleotides, and S-oligos; 4 standard scales for unmodified oligos, and most single labelled DNA-oligonucleotides and 7 standard scales for LightCycler® probes. A comprehensive Synthesis Report comes along with each order, indicating oligo name and sequence, composition of bases, synthesis scale and yield in ODs, µg and nmol, delivery mode (lyophilized or liquid), primer concentration, molecular weight, melting temperature, GC%, purification mode and quality control.

RESEARCH PROJECTS/ACTIVITIES

The Unit is involved in a broad range of medical scientific and diagnostic work, contributing to most of the research projects carried out in the Department of Genetics. Core cooperates with more than 70 researchers within the Research Centre and also from outside e.g. the King Saud University. In last year we generated approximately 16,000 genotyping results and 240,000 sequencing reads.



Number of Samples in SCF

1. DNA Sequencing Requirements

To ensure optimal conditions in the sequencing reactions please try to follow the guidelines set out below:

Template Requirements

Template	Template Quantity	Template Volume
PCR product: 100-200 bp 200-500 bp 500-1000 bp	1-3 ng/µl 3-10 ng/µl 5-20 ng/µl	10 µl per reaction
Single Stranded	25-50 ng/µl	10 µl per reaction
Double Stranded	100-200 ng/µl	10µl per reaction

2. Primer Requirements

The Core provides the following standard (M13F and M13R) primers:

5’ – GTAAAACGACGGCCAGT- 3’ (Forward)

5’ – CAGGAAACAGCTATGACC –3’ (Reverse)

- If you want to use your own primers we need 10µl per reaction at a concentration 1.6 pmol/µl.
- Primers should be re-suspended in dH20. Do not dilute primers in TE. It interferes with the sequencing reaction and will produce poor results.
- If any of your primer is going to be used in multiple reactions, please submit only one tube containing enough volume for all of the reactions.

3. Sample Submission Requirements

- Samples should be labeled clearly and provided in PCR tubes or on 96-well plates with an attached submission form and a gel electrophoresis picture with notation of volumes loaded on the gel.
- If you submit Samples and Primers on 96-well plates, please provide two plates (one for the templates and one for the primers) in the same order.
- Our facility will store your samples for approximately one month. Your samples will be discarded at the end of that time.

Transcriptional Genetics

The transcriptional genetics section is interested in the chromatin and transcriptional regulation of the T-Cell receptor alpha and delta (TCRα/δ) gene locus and the role of the RORγt transcription factor in controlling rearrangement to the TCRα/δ locus, T-cell development, autoimmunity and cancer. We have characterized 5 promoter elements that regulate the recombination activities on the locus. To study the role of some these promoters *in vivo*, we are in the process of generating knock-out/knock-in mice that will shed light on how these promoter exerts their controls over the process of recombination. In addition, we have generated a large pool of thymoma cell lines from the RORγt knock-out mice. We have started analyzing these cell lines for cytogenetic, cell cycle defect, and apoptosis.

HEAD OF UNIT

Abbas Hawwari, PhD

STAFF MEMBERS

Asma Abu-Staiteh

RESEARCH PROJECTS

Project Title: Transcriptional Regulation of TCRα/δ Locus.
RAC Project #: 2080 019
Investigators: *Abbas Hawwari, PhD, Goran Matic (Veterinarian), Edward Hitti, PhD*

Project Progress

Humoral 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 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 TCRβ 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. The proposed studies here are an attempt in this direction.

Project Title: Role of RORγt Transcription Factor in the Immune System Development, Autoimmunity and Transformation.
RAC Project #: 2080 046
Investigators: *Abbas Hawwari, PhD, Goran Matic (Veterinarian), Namik Kaya, PhD, Dilek Colak, Naji Al-Dosari*

Project Progress

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

defects in DP thymocytes, inefficient DP thymocytes development, lack of CP and ILF, enlarged spleen and absence of Th17 cells. Moreover, RORγt is implicated in the development of autoimmune diseases and thymic lymphoma.

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

The Department of

HUMAN CANCER GENOMIC RESEARCH

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 goal 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.

Human Cancer Genomic Research (HCGR), during the year 2009, has excelled in the field of cancer research. Our Director, Dr. Khawla S. Al-Kuraya was awarded the prestigious "King Abdul Aziz award, First Class" on the 11th of January 2010 by the Custodian of the two Holy Mosques, King Abdullah Bin Abdul Aziz in Riyadh, Saudi Arabia. She was awarded this prestigious award for her significant scientific achievements over the years and has made all of us very proud that Dr. Khawla is our Director and that we are a part of her Team. In addition, during the year 2009/2010, HCGR also received three Grant funding for various projects from King Abdul Aziz City for science and Technology (KACST). We were able to publish 12 full length articles in reputable peer-reviewed scientific journals. Integration of three major components of our laboratory studies, (i) Clinical Research using tissue microarray as well as patient's clinical history, (ii) *In-vitro* studies using cell lines to study the functional aspects of these cancers and finally correlating these findings (iii) *In-vivo* using either SCID or Nude mice has greatly improved our chances in better understanding the underlying patho-physiology of cancer. This combined approach has definitely enhanced and improved the chances of treating these cancers using targeted therapy against certain genes that are being discovered with the help of these techniques.

CHAIRMAN

Khawla S. Al-Kuraya, MD, FCAP

SCIENTIFIC STAFF

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ADMINISTRATIVE STAFF

Saad Al-Odaib
Maria Victoria Concepcion
Selah Fulgencio
Myra Maningas

We hope to continue with our research activities in the same fervor and enthusiasm to make 2010, even more productive than last year.

The Department of Human Cancer Genomic Research is further divided into 3 closely inter-related sections:

- Section of Experimental Molecular Pathology
- Section of Molecular Oncology
- Biological Repository Center

SECTION OF EXPERIMENTAL MOLECULAR PATHOLOGY

In 2009, we further expanded our studies to identify and target certain survival molecules that are constitutively activated in cancer. Using tissue microarray technology, we identified c-Met as a survival molecule that is over-expressed in colo-rectal carcinoma, DLBCL and thyroid cancer. We found that certain cancers that over-express this molecule tend to poor prognosis and do not respond to treatment. We are utilizing the latest technology to study these cancers. We are actively collaborating nationally and internationally with other scientific groups to achieve our objectives.

SECTION OF MOLECULAR ONCOLOGY

This department focuses mainly on translational studies, towards developing diagnosis or therapeutic strategies in improving the management of cancer. This is a unique facility and provides unprecedented tools for translational research in the region.

In close collaboration with the section of experimental pathology, we are studying the functional aspects of different cancers with respect to their survival and apoptotic pathways. We are utilizing the data that is being generated by the department of experimental pathology to study in detail, the functional aspects of different genes that are being identified. Using a more specific approach by either using specific inhibitors against these genes or silencing of these genes by siRNA, we are activating different apoptotic pathways that can be used to induce cell death in these tumors. We further confirm these data *in-vivo* by inoculating tumor cells in either SCID or Nude mice and then treat them with the specific inhibitors and follow the progress of these tumors over several weeks.

BIOLOGICAL REPOSITORY CENTRE

The main stay of the biological repository centre (BRC) is the proper preservation & storage of archival frozen tumour and normal tissue samples. DNA and RNA extracted from these frozen samples are being utilized for mutational analysis and differential expression studies in various projects.

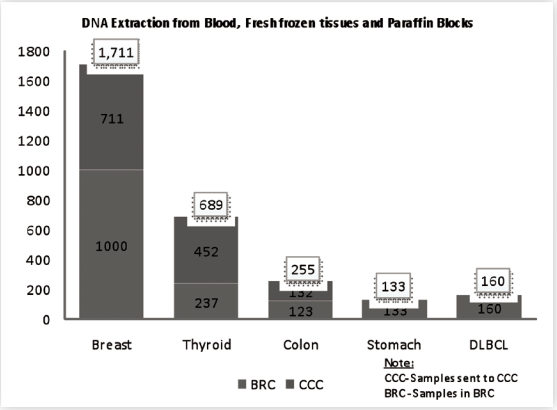
Tasks

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

Activities

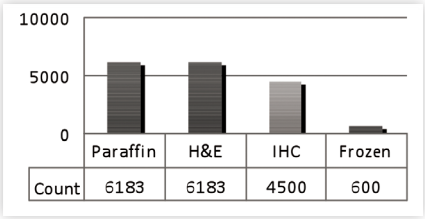
BRC is handling a number of different projects in which biological samples are being optimally stored and further processing is being done as and when requested by the researchers.

1. Processing biomaterial (DNA and/or RNA extraction from blood, frozen tissues and paraffin blocks) for various research projects – a total of 6266 specimens were processed in the year 2009-2010.



2. Cell blocks prepared from cell lines used for immunohistochemistry -40
3. Commercial cell lines acquired from ATCC and other biorepository centers expanded and grown in bulk over 700 vials frozen and stored in liquid nitrogen.

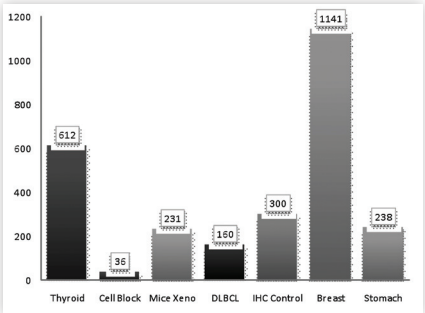
4. Processing of fresh tissue for frozen sections and formalin fixed paraffin embedded (FFPE) tissues from archival paraffin blocks for routine H&E staining and immunohistochemistry. This may include fixation, paraffin embedding, tissue cutting and section staining. Sections are cut and stained for all routine histochemical staining including hematoxylin and eosin.



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

TISSUE MICROARRAY (TMA) UNIT

Department of Human Cancer Genomics Research has established TMA technology and has an extensive archival of tumour specimens in a TMA format. A total of 2,718 tumour and normal tissue specimens were arrayed in a TMA format in year 2009-10. In addition we have 3 cell line block TMA.



RESEARCH PROJECTS

There are three KACST grants and five active RAC approved projects for the year 2009.

KACST Grants

1. Role of c-MET in Saudi Arabian Papillary Thyroid Carcinoma for Novel Therapy.
2. Cyclooxygenases: Target for Epithelial Ovarian Cancer Prevention and Treatment.
3. Prognostic Significance of Genetic Alterations in Saudi Colorectal Cancers.

RAC Approved Projects

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:

- Hematological Malignancies
- Thyroid
- Colon
- Ovary

HEMATOLOGICAL MALIGNANCIES

Project Title: Inhibition of c-MET Is a Potential Therapeutic Strategy for Treatment of Diffuse Large B-Cell Lymphoma

Investigators: *Khawla S. Al-Kuraya, Shahab Uddin, Prashant P. Bavi, Maqbool Ahmed, Abdul K. Siraj, Jehad Abubaker, Azhar R. Hussain, Zeenath Jehan*

Project Description

HGF/c-MET 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 first investigated the role of c-Met in a large series of DLBCL tissues in a tissue micro array (TMA) format. We then followed this with *in vitro* studies on DLBCL cell lines using either pharmacological inhibitors of c-Met or siRNA knock down strategy. c-Met was found to be over-expressed in 73.2% of patients (186/254) and was significantly associated with over expression of p-AKT (p=0.0274), p-GSK3 (0.0047) and Ki-67 (p=0.0012). Interestingly, c-Met over expression was significantly more common in the germinal centre (GC) subtype of DLBCL as compared to activated B cell (ABC) subtype (p=0.0002). Overexpression of c-Met in DLBCL was significantly associated with better survival (p=0.0028) and remained significant in multivariate analysis with IPI thereby confirming c-Met as independent prognostic marker for better outcome in DLBCL. *In vitro*, pharmacological c-Met inhibition and siRNA targeted against c-Met triggered caspase dependent apoptosis. These findings provide evidence that c-Met is an independent prognostic marker for better outcome in Middle Eastern DLBCL. This data also enlightens that c-Met via AKT kinase plays a critical role in carcinogenesis of DLBCL and strongly suggest that targeting c-Met may have therapeutic value in treatment of DLBCL.

Progress

Accepted in Lab Investigation, 2010.

Project Title: Prognostic Significance of XIAP expression in DLBCL and Effect of Its Inhibition on AKT Signaling.
Investigators: *Khawla S. Al-Kuraya, Shahab Uddin, Prashant P. Bavi, Maqbool Ahmed, Abdul K. Siraj, Jehad Abubaker, Azhar R. Hussain, Zeenath Jehan*

Project Description

The inhibitor of apoptosis protein (IAP) family member, X-linked Inhibitor of Apoptosis Protein (XIAP) is essential for cell survival in lymphoma. However, the role of XIAP overexpression in Middle Eastern diffuse large B-cell lymphoma (DLBCL) is not fully elucidated. Therefore, we analyzed the expression of XIAP protein and its clinico-pathological correlation in a large cohort of Middle Eastern DLBCL by immuno-histochemistry in a tissue micro-array format. XIAP was found to be over-expressed in 55% of DLBCL and significantly associated with poor clinical outcome (p=0.0421). To further elucidate role of XIAP in DLBCL and inter-relationship with PI3-kinase/AKT signaling, we conducted several *In vitro* studies using a panel of DLBCL cell lines. We found that pharmacological inhibition of XIAP led to caspase dependent apoptosis in DLBCL cells. We also detected an inter-relationship between XIAP expression and activated AKT in DLBCL cells that may explain cellular resistance to PI3-kinase/AKT inhibition mediated apoptosis. Finally, this anti-apoptotic effect was overcome by simultaneous pharmacological inhibition of XIAP and PI3-kinase/AKT signaling leading to a more potent synergistically induced apoptosis. In summary, our data suggest that XIAP expression is a bad prognostic factor in DLBCL and XIAP-AKT relationship should be explored further as potential therapeutic target in DLBCL.

Progress

Accepted in Journal of Pathology, 2010.

THYROID CANCER

Project Title: Leptin-R and its Association with PI3/AKT Signaling Pathway in Papillary Thyroid Carcinoma.
Investigators: *Khawla S. Al-Kuraya, Shahab Uddin, Abdul K. Siraj, Azhar R Hussain, Maqbool Ahmed, Prashant P. Bavi, Jehad Abubaker, Zeenath Jehan*

Project Description

The putative role of leptin and its receptor (Ob-R) in the pathogenesis of various primary human malignancies has been reported; however, their role in papillary thyroid cancer (PTC) has not yet been evaluated. We investigated the role of Ob-R in a large tissue microarray cohort of PTC followed by *in vitro* studies using a panel of PTC cell lines. Ob-R overexpression was seen in 80% PTCs and was significantly associated with poor disease-free

survival (P=0.0235). PTCs that overexpressed Ob-R showed a aggressive phenotype characterized by older age, extrathyroid extension, larger tumor size, nodal metastasis, advanced stage, tall cell variant histological subtype, and a poor disease-free survival (P=0.0005, P=0.0006, P=0.0398, P=0.0004, P=0.0111, P=0.0003, and P=0.0235 respectively). However, Ob-R expression was not an independent prognostic marker to predict disease-free survival in multivariate analysis. PTCs with overexpression of Ob-R showed a significant direct association with overexpression of XIAP (P<0.0001) and Bcl-XL (P<0.0001). *In vitro* analysis showed that leptin stimulated cell proliferation and inhibited apoptosis via activation of phosphatidylinisitol 3' kinase (PI3K)/protein kinase B (AKT) signaling pathway. Inhibition of PI3K activity by its inhibitor LY294002 abrogated leptin-mediated PI3K/AKT signaling. Gene silencing of Ob-R in PTC cells resulted in downregulation of phospho-AKT, Bcl-XL, and XIAP expression suggesting that leptin-mediated pathogenesis of PTC occurs via involvement of these downstream targets. Altogether, these data show that leptin plays an important role in PTC pathogenesis through PI3K/AKT pathway via Ob-R and is a potential prognostic marker associated with an aggressive phenotype and poor disease-free survival.

Progress

Published in Endocrine related cancer, 2010.

COLON

Project Title: Prognostic Significance of Alterations in KRAS Isoforms KRAS-4A/4B and KRASmutations in Colorectal Carcinoma.

Investigators: *Khawla S. Al-Kuraya, Shahab Uddin, Jehad Abubaker, Prashant P. Bavi, Zeenath Jehan, Azhar R. Hussain, Maqbool Ahmed*

Project Description

Somatic KRAS mutation is an early well-known event in colorectal carcinogenesis but a complete understanding of RAS function and dysfunction in colorectal cancer is still to come. Our aim was to study the incidence of KRAS mutation; KRAS splice variants: KRAS4A and KRAS4B; and their relationships with various clinico-pathological characteristics in colorectal cancer (CRC).In this study, 285 CRC cases were analysed for KRAS mutation by direct DNA sequencing followed by immunohistochemical analysis after validation with real-time PCR assay, to study the protein expression of KRAS4A and -4B isoforms. KRAS gene mutations were seen in 80/285 CRCs (28.1%) and of the mutated cases, the majority of the mutations were seen in codon 12 (81.2%) as opposed to codon 13 (18.8%). CRCs with KRAS mutations were associated with a poor overall survival (p = 0.0009). Furthermore, KRAS mutations at codon 12 were associated with a poor overall survival of 64.4% at 5 years compared with a 5-year overall survival of 75.8% and 78.2% with codon 13 mutation and absence of KRAS mutations, respectively (p = 0.0025). KRAS4A protein expression was predominantly seen in the cytoplasm, while KRAS4B protein was nuclear. KRAS4A overexpression was significantly associated with left colon, histology subtype of adenocarcinoma, p27kip1, and cleaved caspase3 expression. Interestingly, KRAS4A overexpression was associated with a better overall survival (p = 0.0053). On the other hand, KRAS4B overexpression (33.2%) was significantly associated with larger tumour size (p = 0.0234) and inversely correlated with p27kip1 protein (p = 0.0159). Both KRAS mutation and KRAS4A were independent prognostic markers in a multivariate analysis with age, gender, stage, differentiation, and MSI status. Our results highlight the differential role of KRAS isoforms in CRC, their utility as a prognostic biomarker, and underline the importance of KRAS alterations as a potential therapeutic target for CRC.

Progress

Published in Journal of Pathology 2009.

Project Title: Frequent PIK3CA Gene Amplification and Its Clinical Significance in Colorectal Cancer.

Investigators: *Khawla S. Al-Kuraya, Shahab Uddin, Jehad Abubaker, Prashant P. Bavi, Zeenath Jehan, Azhar R. Hussain, Maqbool Ahmed*

Project Description

Using a DNA microarray approach to screen for gene copy number changes in 20 colorectal (CR) carcinoma

samples and filtering for high-level DNA copy number changes, we detected an amplicon at 3q26 containing the PIK3CA gene. Fluorescence in situ hybridization was employed for evaluation of PIK3CA amplification on a progression CR tissue microarray containing 448 CR carcinomas, normal mucosa, and adenomas with follow-up information. PIK3CA amplification (ratio PIK3CA/centromere 3 > or = 2.0) was found in 38% of cancers, while another 19% of tumours had PIK3CA gains (ratio >1.0 but <2.0). Both PIK3CA amplification and gains were associated with high levels of PIK3CA protein expression and no association was seen between PIK3CA amplification and PIK3CA mutation. In a subset of 220 patients who received adjuvant chemotherapy and/or radiotherapy, survival in patients with PIK3CA-amplified cancers was significantly longer compared with patients with cancers without amplification. This association was independent of stage, grade, histology subtype, gender, and age categories. Interestingly, PIK3CA amplification was also seen in CR adenomas, indicating an early genetic alteration, and was also a frequent event in colorectal carcinogenesis. Furthermore, PIK3CA amplification is an independent prognostic marker for better survival and may be one of the promising markers to define CRC subsets that may maximally benefit from adjuvant therapy.

Progress

Published in Journal of Pathology, 2009.

Project Title: Leptin Receptor Expression in Middle Eastern Colorectal Cancer and its Potential Clinical Implication.

Investigators: *Khawla S. Al-Kuraya, Shahab Uddin, Jehad Abubaker, Prashant P. Bavi, Zeenath Jehan, Azhar R. Hussain, Maqbool Ahmed*

Project Description

We investigated the role of leptin receptor (Ob-R) and its relationship with phosphatidylinositol 3-kinase (PI3K)/AKT activation in colorectal carcinomas (CRCs) tissues followed by *in vitro* studies using a panel of CRC cell lines. Obesity serves an important risk factor of several cancers including CRC that ranks as the second most common cancer in Saudi Arabia. High levels of adipokine leptin (Ob) and its Ob-R are seen in obesity and also in various carcinomas including CRC. We investigated the proliferative and antiapoptotic effect of Ob on human CRC cell lines Caco-2, HT-29 and SW-840 and the role of PI3K/AKT-signaling pathway in mediating these actions. Then the expression of Ob-R and its relationship with clinicopathological features was analyzed in 448 CRC, 229 normal colon mucosa and 24 colorectal adenomas using tissue microarray technology. Treatment with Ob resulted in increased proliferation of CRC cell lines and involved activation of PI3K/AKT-signaling pathway. Pretreatment with Ob-R small interfering RNA or PI3K inhibitor inhibited these responses. Ob-R was significantly overexpressed in primary CRC relative to adenomas and normal colonic mucosa. In primary CRC, Ob-R significantly correlated with Ob expression, early stage and well-differentiated tumors. Intriguingly, patient with Ob-R positive tumors showed significantly better overall survival (P = 0.0098). Ob plays a critical role in CRC carcinogenesis through PI3K/AKT pathway via Ob-R. Ob-R is a prognostic marker associated with better survival.

Progress

Published in Carcinogenesis, 2009.

OVARY

Project Title: Overexpression of Leptin Receptor Predicts an Unfavorable Outcome in Middle Eastern Ovarian Cancer.

Investigators: *Khawla S. Al-Kuraya, Shahab Uddin, Maqbool Ahmed, Jehad Abubaker, Abdul Khalid Siraj, Prashant P. Bavi, Zeenath Jehan, Azhar R. Hussain*

Project Description

Background: Recent epidemiological studies have suggested that obesity is associated with ovarian cancer. Obesity hormone leptin and its receptor (Ob-R) contribute to tumor development by enhancing cell growth and survival. This study was design to investigate the prevalence of leptin and Ob-R in Middle Eastern epithelial ovarian cancer (EOC) and to analyze the role of leptin and

the mechanisms under its action in EOC tissue sample and cell lines. ***Methods:*** The expression of leptin and Ob-R was examined by immunohistochemistry in a tissue microarray of 156 EOC samples. Proliferation of EOC cells in response to leptin was assessed by MTT assays, and its anti-apoptotic effects were determined by flow cytometry. Effect of leptin on PI3K/AKT signaling pathway was further determined by western blotting. ***Results***: In clinical samples, Ob-R overexpression was seen in 59.2% EOCs and was significantly associated with poor progression free survival (p = 0.0032). Furthermore, Ob-R expression was associated with anti apoptotic proteins Bcl-XL (p = 0.0035) and XIAP (p = 0.0001). *In vitro* analysis using EOC cell lines showed that leptin stimulated cell proliferation and inhibits apoptosis via activation of PI3K/AKT signaling pathway. Inhibition of PI3K activity by LY294002, a specific inhibitor of PI3-kinase abrogated leptin mediated PI3K/AKT signaling. Gene silencing of Ob-R with Ob-R siRNA in EOC cells resulted in down regulation of phospho-AKT and its down stream targets. ***Conclusion:*** Our findings have potential clinical implication for EOC development and progression.

Progress

Published in Molecular Cancer, 2009.

Project Title: PIK3CA Alterations in Middle Eastern Ovarian Cancers.

Investigators: *Khawla S. Al-Kuraya, Shahab Uddin, Maqbool Ahmed, Jehad Abubaker, Abdul Khalid Siraj, Prashant P. Bavi, Zeenath Jehan, Azhar R. Hussain*

Project Description

Background: PI3K/AKTsignaling pathway plays an important role in cell growth, proliferation, and tumorgenesis 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. ***Results:*** Fluorescence in situ hybridization (FISH) technique and DNA sequencing were used to analyze PIK3CA amplification and mutation respectively. Expression of PIK3CA protein expression (p110 alpha), 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 alpha overexpression was associated with increased phosphorylation of AKT-Ser 473 and with the proliferation marker Ki-67. ***Conclusion:*** 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

Published in Molecular Cancer, 2009.

FUTURE DIRECTION AND RESEARCH

Human Cancer Genomic Research will continue on our main focus on identifying and targeting molecular targets, especially, those signaling molecules that are over-expressed in cancers of Middle Eastern origin. Complementing clinical research with Basic scientific studies including *in-vitro* functional assays and in-vivo animal models will further enhance our research in the field of cancer These studies will definitely help in improving the over-all survival of patients suffering from these cancers. Within our research laboratory, we will continue using state-of-the-art approaches to study fundamental questions regarding cancer in Saudi Arabia and the Middle East. In addition to Basic research, there is also a strong emphasis on translating basic science advances into more effective and highly reliable diagnostic and therapies.

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The

RESEARCH CENTRE
TRAINING & EDUCATION OFFICE

Research Centre
Training & Education Office

The Research Centre Training and Education Committee (RCTEC) was formed to formulate guidelines & procedures to provide and administer the training and education activities in the Research Centre. RCTEC oversee the Research Centre Training Education Office (RCTEO) in facilitating the following:

- In-Kingdom and Out-Kingdom scholarship training and education - leading to higher education which support students to prominent institutions to certify with the advancement of technology
- In-House Training in progressive fields of science and technology
- Summer Training Programs such as:
  - Future Scientist - a program that will assist talented young male high school Saudi nationals in the acquisition of scientific skills and to prepare them for a future in the field of Biomedical Sciences
  - Ibn Sena - a program that will assist talented young Saudi nationals to integrate their scientific skills/talents in preparing them in different areas of Science in the future
  - Al-Razi Summer Program that will expose the undergraduate students to the work environment and give them the chance to get hands-on training in the basic science
- Special Courses, Workshops, Symposia and other events are conducted by RCTEO throughout the year.

DIRECTOR

Refaat Al-Mazrou, MSc, MIPEM

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EXPERTISE

The RCTEO assists external training and education for Saudi citizens who wish to pursue MSc, PhD degrees and Postdoctoral Fellowship. Affiliations with reputable scientific and educational local and international institutions have been established to ensure that the latest technology is acquired, hence career development is advanced.

ACTIVITIES

The Research Center Training and Education Committee and its office administer the following programs:

Postdoctoral Fellowship Program
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.

Recipient	On-Board	Completed
PhD	3	0

Hospital Scholarship Program
The Institution helps qualified employees to pursue their studies and obtain a higher degree or gain practical experience in their field, to serve the needs of KFSH&RC. The primary objective of this program is to raise the overall educational and healthcare standards at KFSH&RC by encouraging employees to develop their academic and technical skills. The scholarship can be given either as Out-of-Kingdom Study Program or In-Kingdom Study Program.

Recipient	On-Board	Completed
PhD	11	0
MSc	4	1
BSc	2	1

In-House Research Graduate (for Non-RC Employees)
This program is for MSc and PhD students from local or international universities who are interested in conducting their research project in the Research Centre under joint supervision with their university.

Research Student	On-Board	Completed
PhD	4	0
MSc	8	0

In-House Training Program for Non-RC Employees (IHTP)
The Research Centre provides training opportunities for eligible candidates from other institutions for a maximum of six (6) months. These include:

- Undergraduate students who are seeking training related to their university degree
- Individuals who are seeking training to enhance their qualifications
- Saudi employees from public and private sectors who want to develop an aptitude for research
- Recipients of fellowships sponsored by international institutions such as the International Atomic Energy Agency (IAEA) seeking on-the-job training
- 1.4.5. 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
I-H TP	84	83

Future Scientists Program (FSP)
The aims 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	16

Ibn Sena Program (ISP)

An agreement was created in 2006 between KFSH&RC-Research Centre and King Abdulaziz and his Companion Foundation for Giftedness & Creativity 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
ISP	27

Al Razi Summer Training Program (ARSTP)

The RC-TEO encourages cooperation with national institutes for the exchange of information and pursuit of knowledge in an organized and productive manner. The objectives of this program is to expose the undergraduate students to the work environment and give them the chance to get hands-on training in the basic science and to show their abilities and find out their suitable field of science in the future.

Program	Completed
RCS	32

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	32

Workshops and Conferences (WS&Conf)

The Research Centre Training and Education Office organizes a number of annual workshops, conferences and special courses/events in specific fields of science.

Date	Courses	No. of Participants
10 -12 Nov	SPECT/CT Course & Workshop; Fundamentals, instrumentation & Techniques	180
03 – 05 Oct	2nd Introductory Course to Mass Spectrometry and Proteomics Workshop	32
25 – 27 May	Introduction to Cell and Molecular Biology Course	20
9 -12 Mar	Innovative Approaches in Radiotherapy: Beyond Tomorrow	600
April 8-6	PACS Administrator Course	159
25 – 27 Apr	Biostatistics Research Methods Course	43
21 – 25 Feb	Recombinant DNA Methodology	10

The

Medical and Clinical Affairs

Report

The Department of

DENTISTRY

Dentistry

PROJECT TITLE	INVESTIGATORS	RAC#
Pattern of Craniofacial Anomalies seen in a tertiary care hospital, Riyadh, Saudi Arabia	Aziza Al Johar, Kandasamy Ravichandran, Shazia Subhani	991030
Registry of Cleft Lip/Palate and Craniofacial Anomalies	Aziza Al Johar, Kandasamy Ravichandran, Shazia Subhani	991030
Modeling familial aggregation of Cleft lip/palate: A hospital based registry study	Ravichandran Kandasamy, Aziza Al johar, Mohamed Shoukri, Yasmin Al Twaijri, Shazia Subhani	2101004
Measurement of Treatment Outcome in Cleft Lip and Palate Patients	Aziza Al Johar	2091017
Genetics of Craniofacial Birth Defects in Saudi Arabia	Fouzan Al Kuraya, Aziza Al Johar	2080006
The Incidence of Oral Mucositis in Pediatric Hematopoietic Cell Transplantation at KFSH&RC	Zikra AlKhayal, Mouhab Ayas, Mohammed Al Helal, A. Al Jefri, A. Al Seraihi, RN Mohamed	2091015
Rare Dental Disorder Registry	Adeeb Al Omrani, Hans Hansson, Richard Hakansson, Khalid Al Zoman, Shazia Subhani	2071082
Gene Expression & Immuno-histological findings in patients with Papillon Lefèvre Syndrome	Adeeb Al Omrani, Saleh Al Muhsen, Hamad Al Zaidan, Mohammed Al Owain, Richard Hakansson, Christer Ullbro	2070022

CHAIRMAN

Abdulhadi Abanmy, BDS, DMSc

THE SECTION OF PEDIATRIC DENTISTRY

Project Title: Pattern of Craniofacial Anomalies Seen in a Tertiary Care Hospital, Riyadh, Saudi Arabia.
RAC Project #: 991030
Investigators: *Dr. Aziza Al-Johar, Dr. Kandasamy Ravichandran, Ms Shazia Subhani*

Project Description

Abstract

Objective: To report the patterns of craniofacial anomalies in Saudi Arabia.
Design and setting: Data from a hospital registry, based at a tertiary care center.
Patients: Craniofacial patients registered during 2002-2008 in the Cleft lip/palate and craniofacial anomalies registry at King Faisal Specialist Hospital & Research Centre, Riyadh.
Results: Out of the 411 craniofacial cases (M=223; F=188), 168 cases had cranial anomalies, 311 cases had facial anomalies with 68 cases overlapping both the conditions. Craniosynostosis, accounting to 33.1% of total cases, was seen in 75 male and 61 female. Out of the 66 cranial syndromic cases, Apert syndrome and Crouzon syndrome was seen in 25 and 18 cases, respectively. Among facial anomalies, Dysmorphic features were often observed (35) followed by protruded premaxilla (20) and micrognathia(18). Among facial syndrome, Pierre Robin sequence (66), Goldenfar syndrome (18) and Van der Woude syndrome(16) was observed. Among associated deformities of CL/P, cleft palate (160; 57.8%) was more common, followed by cleft lip and palate (87; 31.4%) and cleft lip (23; 8.3%). Out of the 208 cases having other congenital anomalies, cardiovascular is the most commonly affected system with 34 children. Significantly (p=0.01) more family history of anomalies was observed in children born to parents whose marriages among first cousin than in children born to parents whose marriages were not among first cousin.
Conclusion: The pattern of craniofacial anomalies observed in this study does not differ significantly from those reported in the literature.

Progress

Submitted for publication in the Saudi Medical Journal, Dec 2009

Project Title: Registry of Cleft Lip/Palate and Craniofacial Anomalies.
RAC Project #: 991030
Investigators: *Dr. Aziza Al-Johar, Dr. Kandasamy Ravichandran, Ms Shazia Subhani*

Project Description

Background: The King Faisal Specialist Hospital & Research Centre(KFSH&RC), established a cleft lip with our without cleft palate (CL/CP) registry and started collecting data on CL/CP patients attending the Department of Dentistry, KFSH&RC since mid-1999. The registry is a coordinated collaboration between the Department of Dentistry and Department of Biostatistics, Epidemiology and Scientific Computing (BESC). The CL/CP registry is being expanded to include craniofacial anomalies in it scope and hence, the name of the registry is being changed from Cleft Lip/Palate Registry to Registry of Cleft Lip/Palate and Craniofacial Anomalies.
Rationale: Treatment including multiple surgeries, speech therapy, and dental and orthodontics of cleft lip and palate have developed very rapidly, but the epidemiological study for cleft lip and palate remains in its infancy. The registry is an early warning system for discovering excessive occruences of craniofamial anomalies and is the foundation for the epidemiological research needed to evaluate the clusters.

KFSH&RC is one of the major referral hospitals in the Kingdom. The development of a Craniofacial Anomalies Registry (in the absence of such a population-based registry) at KFSH&RC will be an important source of data on this congenital defect in the Kingdom.

Progress

The project is ongoing.

Project Title: Modeling Familial Aggregation of Cleft Lip/Palate: A hospital-Based Registry."
RAC Project #: 2101004
Investigators: *Dr. Ravichandrean Kandasamy, Dr. Mohamed Shoukri, Dr. Yasmin Al Twaijri, Dr. Aziza Al-Johar, Shazia Subhani*

Project Description

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

The proposed study is based on the data, without patient's identification detail, from the Cleft lip/palate and Craniofacial Anomalies Registry.

Objectives
- To examine similarity among pairs of sibling for each of the two traits (cleft lip or palate)
- To assess elevation in the risk of disease for a single sib conditional of the fact that the other sib has attained the same disease condition, accounting for the within cluster correlation
- To assess the possible effect of consanguinity and gender on the risk of cleft lip/palate.

Method
Maximum likelihood estimation method will be used to estimate the model parameters and standard errors of the estimates will be derived.

Project Title: Measurement of Treatment Outcome in the Cleft Lip and Palate Patients in King Faisal Specialist Hospital & Research Centre, Saudi Arabia.
RAC Project #: 2091017
Investigator: *Dr. Aziza Al Johar*

Project Description

Cleft lip and palate is the most common birth defect worldwide. Clefts of the lip and/or palate (CLP) are a congenital anomaly and among the most common birth defects worldwide, presenting in wide variety of forms and combination. The majority are non-syndromic where CLP occurs in isolation of other phenotypes. Cleft lip and/or palate consider syndromic when one or more additional features are involved.

The principal management of the KFSH interdisciplinary cleft team is to produce a child that looks normal, speak and hear normally with improved facial appearance. The team aimed at physical rehabilitation stressing the fact that the best treatment should ensure a good aesthetic and functional outcome.

The main purpose of this study is to evaluate the clinical outcome of the treatment of unilateral cleft lip and palate children who were treated at King Faisal Specialist Hospital since 1999, in order to improve quality of care.

Specific Aims & Objectives
- To evaluate the clinical outcome of cleft care at KFSHRC
- To identify risk factors for poor outcome
- To address the health needs of these patients
- To have periodic evaluation of cleft records and protocol

Objectives of the study
- To examine existing records using different clinical tool
- To collect records of different clinical outcomes for cleft children
- To compare the KFSHRC's outcome result with the result from developed countries

Method

The study will be retrospective – case control study.

Sample

The sample study population consist of 150 unilateral cleft lip and palate children who were treated at KFSHRC from 1999 to 2007.

Project Title: Genetics of Craniofacial Birth Defects in Saudi Arabia.

RAC #: 208-0006

Investigators: *Dr. Fouzan Al Kuraya, Dr. Aziza Al Johar*

Project Description

Birth defects are important cause of disability worldwide with tremendous impact on the public health system. Craniofacial birth defects are particularly important because, as a group, they represent the second most common class of birth defects in humans. Additionally, they affect a region in the body that's readily observable by others thereby compounding the psychological component of the disability. The cause of most birth defects is unknown. Genetic, nutritional, infectious, and other environmental factors, contribute to the total incidence of birth defects, but the percentage attribute to each is not known. In Saudi Arabia several factors make it likely that genetic etiologies contribute more significantly to craniofacial birth defects than other parts of the world. Perhaps the most important of these factors is the high frequency of autosomal recessive disorders (many of which will inevitably involve the complex structure of the face and other craniofacial structures) as a result of high degree of inbreeding and consanguinity. One research group has an extensive experience in mapping mendelian disorders, including genetic conditions associated with craniofacial anomalies. Similarly, we have solid expertise in the areas of clinical, molecular and developmental genetics. We propose to focus our existing expertise direction of dissecting the molecular defects that underline craniofacial birth defects in Saudi Arabia. Characterizing these mutations will have an obvious impact on the medical care of the affected individuals since it makes prenatal/pre-implantation diagnosis available options but it also represents a step in the right direction toward the implementation of gene therapy in conditions that are amenable to this approach. From an academic standpoint, the study of birth defects, craniofacial birth defects included, has proven indispensable to human genetics research. Biomedical literature is replete with high profile examples where the understanding of the genetic etiology of a given birth defect was key to the discovery of highly important genes and pathways that propelled our understanding of how genes eventually control the making of a physical human being. Consequently, our group has a keen interest in understanding how different mutations affect the protein function of the respective genes. Furthermore, new genes identified in the course of this work represent an existing opportunity to better understand the molecular mechanisms that govern the formation of the craniofacial structures by studying their expression pattern and protein function. Given the scope of this project, the methodology will not only include linkage analysis but will also use the latest available tools in developmental and molecular genetics. This is a five year project genetic underlying defect.

Aims of the Proposed Study

- To identify the genetic lesions (mutations) that underline the various genetic forms of Carniofacial birth defects in the Saudi population.
- To study the role of the identified genes in the model organism.

Project Title: The Incidence of Oral Mucositis in Pediatric Hematopoietic Cell Transplantation.

RAC #: 2091015

Investigator: *Dr. Zikra AlKhayal, Dr. Mouhab Ayas, Dr. Mohammed Al Helal, Dr. Abdullah Al Jefri, Dr. Amal Al Seraihi, RN Amal Mohammed*

Project Description

Abstract

Oral Mucositis is one of the most common and debilitating forms of Mucositis and often arises from high dose chemotherapy and radiotherapy. It is reported that seventy to eighty percent of patients undergoing hematopoietic cell transplantation (HCT) suffer from oral Mucositis during cancer therapy. The objective of the study is to

evaluate prospectively the incidence of oral mucositis in pediatric patients aged 0 to 14 years receiving myeloablative conditioning regimens and hemtopoietic cell transplantation at the bone marrow transplant unit at King Faisal Specialist Hospital & Research Centre. The results of the study will address the extent of oral mucositis in the bone marrow transplant unit and if there is a need for future management plans to improve the quality of life and provide optimal care for this special group of pediatric patients.

Specific aims and objectives

- To assess prospectively the incidence of oral mucositis in the pediatric population receiving hematopoietic cell transplantation (HCT) at King Faisal Specialist Hospital & Research Centre-Riyadh.
- To evaluate the factors predicting oral mucositis severity and correlation with disease category, conditioning regimen, type of transplant and delayed absolute neutrophil recovery.
- The outcome of oral mucositis and relation between grade severity, reported pain, ability to eat, saliva production and analgesic use.

Method

The study will be a prospective cross-sectional, case-control study.

Patients

The sample study population will consist of all pediatric patients age 0 to 14 years old undergoing hematopoietic cell transplantation at King Faisal Specialist Hospital & Research Centre during the study period October 2009-October 2010.

Progress

The project is ongoing.

THE SECTION OF PROSTHODONTICS

Project Title: Rare Dental Disorder Registry.
RAC Project #: 2071082
Investigators : *Dr. Adeeb Al Omrani (PI), Dr. Hans Hansson, Dr. Richard Hakansson, Dr Khalid Al Zoman, Ms Shazia Naz Subhani*

Project Description

Abstract

Congenital Oral Anomalies are a broad category of health conditions that are present at birth and are a deviation from normal anatomic growth, development, or function. There is an urgent need to increase knowledge about oral rehabilitation for people with oral/dental disabilities and new methods for treatment must be developed and evaluated. This will lead to better care and will have great influence on the quality of life for people with oral disabilities.

The aim of this registry is with a multi disciplinary team approach enhancing the opportunities for individuals with rare-oral and facial disorders to get adequate information, diagnosis and treatment at King Faisal Specialist Hospital & Research Center, from all over the country.

Progress

The project is ongoing.

Project Title: Gene Expression & Immuno-Histological 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, Christer Ullbro, DDS, PhD*
Research investigators: *Namik Kaya, PhD **(Co-PI)**, Dilek Colak, PhD, Said Dermime, PhD, Hazem Ghebeh, PhD*

Project Description

Abstract

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

in the cathepsin C (CTSC) gene in this population. The aim is to study the histopathology, immunological profile, and gene expression of PLS from blood samples and gingival biopsies; and thus shed more light on the pathophysiology of the disease and explore whether new subclasses of this disease can be identified based on gene expression profiles. Furthermore, we aim to establish a preventative program among this high-risk group through carrier testing and genetic counseling. The study will include 40 PLS patients presented at the dental department in KFSH&RC, retrospectively. A correlation may be found between the immunological status/gene expression and level/severity of periodontal infection. This may give more insight on the role of cathepsin C in the disease.

Aims

Our aim in this study is to perform a thorough genetic and immunological evaluation in a cohort of Saudi patients with PLS from the following aspects:

- 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.

Progess

The project is ongoing.

The Department of

EMERGENCY MEDICINE

Emergency Medicine

The department undertook many research projects during year 2009. The department surpassed its objectives for research this year. The set objective was 2 researches and 2 publications whereas there were 10 completed research projects (3 were published) and 3 chapters in different books were written. Six abstracts were accepted at international conferences for presentation. The highlight of the year 2009 was an award won by Dr Abeer Omar Ghawanni (Resident Emergency Medicine) for the presentation of an abstract at the Emergency Medicine Resident Research Day (Feb 2010) for our study on “Impact of Consultation on Patients Length of Stay in Emergency Department”. This abstract was also accepted at ACEP for presentation in October 2010.

RESEARCH COORDINATOR

Hameed Ullah Khan, MD

RESEARCH ACTIVITIES

Project Title: Stroke as Initial Presentation in Pediatric Neurosarcoidosis.
Investigators: *Al Qasim Ghada, AlMogbil, Qureshi Nadeem*

Objective: To describe a case of stroke as being the initial clinical manifestation in a child with sarcoidosis having no previous neurological involvement.
Design: Case study.
Setting: King Faisal Specialist Hospital and Research Centre.
Study population/sample: One patient presentation.
Main results: The patient was known to have sarcoidosis. Sarcoid granulomas can affect virtually any part of the central and peripheral nervous system. Stroke is an extremely rare presentation of neurosarcoidosis especially in pediatric population.

Project Title: Validity of CTAS in Tertiary Care Hospital in Saudi Arabia.
Investigators: *Ayad AlDarrab MD, Ghada Omar Bakhider MD, Abeer Omar Ghawanni MD, Nadeem Qureshi MD*

Project Title: Prognostic indicators of pediatric near drowning in Saudi Arabia
Investigators: *AlFaifi M, Hijazi N, AlGhamdi F, Alamri W, Alghamdi A, Kordi A, Qureshi N*

Objective: To identify various factors associated with neurological outcome in near drowning patients.
Design: Retrospective study.
Setting: King Abdul Aziz Medical City Hospital.
Study population/sample: Those patients who were admitted to King Abdul Aziz Medical City Hospital during past 7 years with near drowning. Good outcome meant no neurological deficit on discharge.
Main results: A total of 31 patients were recruited in the study. Good outcome was seen in 48% (15) of the patients. Fifty two percent (16) had bad outcome. The factors associated with good outcome were pre hospital CPR, pupillary response to light, pH >7, GCS >9, and blood sugar <10mmol/l.

Project Title: Impact of Consultation on Length of Stay in Emergency Department.
Investigators: *Nadeem Qureshi MD, Abeer Omar Ghawanni MD, Ghada Omar Bakhider MD, Ayad AlDarrab MD*

Project Title: Consultation Patterns in an Emergency Department of a Tertiary Care Hospital.
Investigators: *Nadeem Qureshi MD, Abeer Omar Ghawanni MD, Ghada Omar Bakhider MD, Ayad AlDarrab MD, Khalid AbuHaimed MD*

Project Title: Sports Diving Practices and Accidents in Saudi Arabia.
Investigator: *Ghada Omar Bakhidar, MD*

Project Title: Caregivers in Arabia Do Not Give Their Children With Fever the Accurate Dosing of Acetaminophen.
Investigators: *Fawaz A Enzi MD, Nahar Al Rowaily, Dr Mohammad Al Omar.*

Objective: Whether caregivers of the children presenting at King Faisal Specialist Hospital Emergency Department give their children accurate dose of acetaminophen and to assess factors associated with dose inaccuracy.
Design: Prospective cross sectional study.
Setting: Pediatric Emergency Medicine Department King Faisal Specialist Hospital and Research Centre.
Study population/sample: All children under 14 years who receive acetaminophen within the last 24 hours. Study was conducted over a period of 6 months.
Main results:

- Caregivers who gave the accurate doses were most likely to give acetaminophen doses in less than 4 hours. (RR 0.63, P 0.04, 95% CI = 0.37-1.07)
- Patients who received acetaminophen per rectum had a significantly greater rate of supra-therapeutic doses 9/28 (32%) versus oral route 39/149 (26%) respectively 95% (CI=0.14-0.48)
- Caregivers with secondary and intermediate education levels were more likely to give an accurate dose.

Project Title: Pediatric Residents' Knowledge of Evidence Based Medicine: A pilot Study.
Investigators: *Alshabanah H., Paes B., Mosalli R*

Project Title: Procedural Skills Training During Emergency Medicine Training Residency: Are We Teaching the Right Things? International Perspective from Saudi Arabia.
Investigator: *Nadeem Qureshi*

Objective: The objective was to assess whether the skills training program at Denver health Residency program was teaching the right skills to the residents.
Design: Cross sectional survey.
Setting: Denver University Emergency Medicine
Study population: Past 10 year graduates.
Methods: A web based survey was sent to all graduates of the Emergency Medicine Denver Health Residency Program over the past 10 years.
Main results:

- Seventy four percent (59% of those eligible) completed the survey. There were significant discrepancies between importance in practice and preparation during residency for 8 of the 12 skills trained at the program.
- There were strong correlation (r>0.3) between preparation during residency and confidence for 10 of the twelve procedural skills suggesting a high degree of internal consistency for the survey.

Project Title: Chest Pain in a 12-Year Old Boy: When is it a Harbinger of Poor Outcome?
Investigators: *Hisham Alomran, Faisal AlGhamdi, Fadia AlKhattabi*

PUBLICATIONS

- Sickle cell disease in children. Nadeem Qureshi MD, Stephen Gletsu and Mohammed AlMogbil MD. *Harwood-Nuss' Clinical Practice of Emergency Medicine*. Fifth Edition (2010) Edited by Allan B. Wolfson. Published Lippincott Williams & Wilkins. Pages 1332-1337.
- Premature infants in the emergency department. Nadeem Qureshi MD, Stephen Gletsu and Mohammed AlMogbil MD. *Neonatal and Infant Emergencies* (Published 2009) Edited by Ghazala Sharieff and Maureen McCollough. Published by Cambridge University Press. Pages 16-25
- Sickle Cell Emergencies. Nadeem Qureshi MD, Stephen Gletsu and Mohammed AlMogbil MD. *Neonatal and Infant Emergencies* (Published 2009) Edited by Ghazala Sharieff and Maureen McCollough. Published by Cambridge University Press. Pages 235-242

AWARDS

Dr Abeer Omar Ghawanni (Resident Emergency Medicine) received the award for the best Abstract at the Emergency Medicine Resident Research Day (Feb 2010) for our study on "Impact of Consultation on Patients Length of Stay in Emergency Department". This abstract has also been accepted at ACEP for presentation in Oct 2010.

The Department of

FAMILY MEDICINE AND POLYCLINICS

Family Medicine and Polyclinics

CHAIRMAN

Abdullah Alkhenizan, MD

Research is highly supported as a key component of the academic programs in the Department of Family Medicine and Polyclinics. There is a Research Committee which is mainly charged with facilitating and coordinating the research activities within the Department of Family Medicine and Polyclinics. As many as possible of department staff are encouraged to be involved in research either independently or collaboratively with other medical departments' staff or Research Centre scientists. There is a plan to restructure the Research Committee into a Research Unit with the following objectives:

- To increase availability of resources, e.g. technical, financial, personnel, expertise.
- To provide special compensation and/or awards in terms of time or money for researchers who completed distinguished researches and publications.
- To provide logistic support to researchers in presenting completed researches in national and international meetings and conferences.
- To work with ICIS, Medical Records, Quality Management Department staff to translate hospital information and medical records systems supportive to collect clinical data for research studies.

It is projected that Department staff would be more pro-active in converting the huge volume of available clinical data into research studies that will enhance their professional expertise and ultimately contribute to achieving the highest standards of patient care in King Faisal Specialist Hospital and Research Centre (Gen. Org).

RESEARCH ACTIVITIES

Project Title: The Rrole of Gene Polymorphism in the Regulation of the Thyroid Stimulating Hormone Levels.
Principal Investigator: *Nduna Dzimiri, PhD*
Co-Principal Investigator: *Ali S. Alzahrani, MD*
Co-Investigators: *Abdullah Al Khenizan, MD, Maha Al Rasheed, Ms Pharm, Abdulraof Ahmad Al Mahfouz, MD Jalal Jalaluddin, PhD, Abdullah Al-Khenizan, MD*

Project Title: Detection of Interferon Gamma Production for the Diagnosis of Latent Tuberculosis in Healthcare Workers at KFSH&RC.
Principal Investigators: *Shal Al Hajoj, PhD & Abdulrahman Al Rajhi, MD*
Co-investigators: *Ali Alzahrani, MD, Sahar Al-Thawadi, MD, Abdullah Al Khenizan, MD, Abdulaziz Al Nasser, MD, Abdulaziz Al Saif, MD, Kevin Hafez, MD*
Ali Alzahrani, MD, Sahar Al-Thawadi, MD, Philip Taylor, Haifa Al-Talhi

Project Title: Impact of Accreditation on the Quality of Health Care Services: A Systematic Review of the Literature.
Principal Investigator: *Abdullah Al Khenizan, MD*
Co-Investigator: *Prof. Charles Shaw*

Project Title: Assessment of CBAHI Standards Against ISQua Principles for Healthcare Atandards.
Principal Investigator: *Abdullah Al Khenizan, MD*
Co-Investigator: *Prof. Charles Shaw*

Project Title: Use of Folic Acid in Saudi Female Population.
Principal Investigator: *Patricia McWalter, MD*

Project Title: Swyer James Macleod Syndrome.
Principal Investigator: *Patricia McWalter, MD*

PUBLICATIONS

- Efficacy of steroids or acupuncture for Bell's palsy. Amer Sheikh, MD; Abdullah Alkhenizan, MD; *Acupunct Med*. 2010 Mar;28(1):56.
- Transient Osteoporosis of the Hip. Patricia McWalter, MD; Ahmed Hassan, MD; *Ann Saudi Med* 2009 29(2): 146-148
- Gender effects in blood pressure, anthropometric measures, c-reactive protein, LDI oxidation and Apolipoprotein E genotypically determined blood serum lipd and lipoprotein concentrations responsiveness to flaxseed oil supplementation in type 2 diabetics (submitted for publication). Co-Author: Kevin Hafez, MD.
- The roles of apo E genotype, gender and adipokines in blood plasma lipids in Caucasians with well-controlled type 2 diabetes (co-author: Dr. Hafez; in press for *Int J of Diabetes and Metabolism*).
- Only a fraction of T-B-NK +SCID and Omenn's Syndrome is demarcated by RAG1 and RAG2, but not Artemis, mutations in Arab population (accepted for publication in *J Allergy Clin Immunol*). Co Author: Rand Arnaout, MD.
- Adenosine deaminase deficiency among SCID in Saudi Arabia. Co Author: Rand Arnaout, MD.
- JAK3 genetic lesions are mainly responsible for the T-B+NK-SCID in Saudi Arabia. Co Author: Rand Arnaout, MD.
- Molecular genetic defects of Omenn's Syndrome in Saudi Arabia. Co Author: Rand Arnaout, MD.
- Underlying Molecular Genetic Defects of SCID in Saudi Arabia. Co Author: Rand Arnaout, MD.
- A novel mutation in purine nucleoside phosphorylase in a child with a normal uric acid level. Co-Author: Rand Arnaout, MD.
- Allogenic stem cell transplantation in patient with major histocompatibility complex class II immunodeficiency: a single experience (abstract). Co Author: Rand Arnaout, MD.
- Chorioretinal lesions in patients with CGD-ease series (accepted for publication in J Am Assn for Ped Ophthal and Strabismus. Co Author: Rand Arnaout, MD.
- Allogenic stem cell transplantation using myeloablative and reduced intensity conditioning in patients with major hiscompatibility Complex class II deficiency (abstract, ESID). Co Author: Rand Arnaout, MD.
- Molecular and clinical profile in a large cohort with chronic granulomatous diseases from Saudi Arabia (accepted for publication in BMT). Co Author: Rand Arnout, MD

The Department of

LIVER TRANSPLANT & HEPATOBILIARY & PANCREATIC SURGERY

Liver Transplant & Hepatobiliary & Pancreatic Surgery

The members Department of Liver Transplantation & Hepatobiliary-Pancreatic Surgery are involved in different research activities in the hospital, combined with other department such as Section of Medical Oncology (RAC # 2091 040). Articles were published in the year 2009 in both local and international journals. Abstracts were accepted and presented in well-recognized international congress such Asian Pacific Association for Study of Liver Disease, European Association for Study of Liver Disease and International Liver Transplant Society. Research projects involve both Transplant Hepatology and Transplant Surgery in addition to Donor issues, with special emphasis on ideas that help the program development. The department is still waiting for RAC approval for some research proposals.

CHAIRMAN

Mohammed Al Sebayel, MD

RESEARCH ACTIVITIES

Project Title: Pan Arab Liver Transplantation Registry.
RAC Project #: 2071 022
Investigators: *Hatem Khalaf, MD, Mohammed Al Sebayel, MD*

Project Description

Establishing a web-based Liver Transplantation registry aiming to monitor Liver Transplantation activities in KFSH& RC and towards the Arab World hoping for better follow-up and care for liver transplant patients. The project objectives include the following:

1. To obtain the frequency of liver transplantation activity in KFSHR&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 2009:

- 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): Riyadh Military Hospital approved to incorporate their liver transplant patients data to the registry, however, due to re-organization in their administration staff this has been put on hold.
- Phase III (Liver Transplant patients in Arab World): Cairo University updates liver transplant patients' data in the registry in a timely manner.

The

ONCOLOGY CENTRE

Oncology Centre

KFSH&RC enjoys the recognition of having the largest cancer facility in the Gulf region where more than 2,500 new patients are treated annually. Established with a mission of providing excellent cancer treatment, education and research, the Oncology Centre evolved over the years towards its vision of becoming one of the best international centres for cancer research, prevention, and treatment. Accredited by the World Health Organization (WHO) as a Collaborating Centre for Cancer Prevention and Control, cancer patients are assessed in multidisciplinary clinics and provided with treatment in accordance with disease specific internationally accepted management guidelines. Our oncologists continue to actively address national oncology problems through their involvement in institutional, national, and international research protocols with the invaluable support of the Centre's Research Unit which also serves as a hospital base for cancer and bone marrow transplantation registries. Major achievements for the year include:

- Medline indexing of the publication of the KFSHRC Hematology/ Oncology and Stem Cell Therapy Journal.
- Continued membership of the CBMTG (Canadian Bone Marrow Transplantation Group) and the EBMT Clinical Trials Group (EBMTG); Highest accruing institution on CBMTG protocol 0601.
- Continued institutional membership and collaborative studies with Southwest Oncology Group (SWOG), American College of Radiology Imaging Network (ACRIN), and Radiation Therapy Oncology Group (RTOG).
- Several collaborative studies started with RTOG. Highest accruing institution on RTOG protocol 0417.
- Eastern Mediterranean Blood & Marrow Transplantation Group (EMBMT) established. Phase I & II completed, Phase III in progress. Second article published in Bone Marrow Transplantation Journal.
- Twelve new research studies started; several studies completed and 29 papers were published.

DIRECTOR

Mohammed Mohiuddin, MD

DEPUTY DIRECTOR

Mahmoud Aljurf, MD

- Four disease specific database/registries opened for rectal cancer, Hodgkin's, Non-Hodgkin' s and Hemophilia.
- Five clinical protocols established in epithelial ovarian cancer, breast cancer, renal cell carcinoma, and myeloid leukemia.
- Gulf Oncology Regional Group (GORG) established in KFSH&RC. The first successful study GORG-001 completed. Launched the second multicenter study as GORG-002.
- Continue to receive investigational drugs from National Cancer Institute (NCI) for patients on clinical trials.
- Intensity Modulated Radiation Therapy (IMRT) credentialing by Radiological Physics Center (RPC) at MD Anderson Cancer Center, USA.

FUTURE RESEARCH DIRECTION

- Promote well designed clinical/transitional research activities.
- Establish firm collaboration and team work with Research Center and other local, regional and international groups 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 technologies to provide the most advanced and optimum cancer treatments.
- Ensure continuous availability of emerging and evolving therapies and drugs through clinical trials at KFSH&RC.

RESEARCH UNIT ON-GOING RESEARCH PROJECTS/PROPOSALS

1. CBMTG 0601: A Randomized Multicentre Study Comparing GCSF Mobilized Peripheral Blood and GCSF stimulated Bone Marrow in patients Undergoing Matched Sibling Transplantation for Hematologic Malignancies. RAC # 2081 076. M. Aljurf.
2. 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. F. Alsharif, N. Chaudhri.
3. 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. A. Al Sayed.
4. 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. T. Twegieri.
5. 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. T. Twegeiri.
6. 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. N. Al Rajhi.
7. RTOG 0227 – Phase I/II Study Of Pre- Irradiation Chemotherapy With Methotrexate, Rituximab, And Temzolomide And Post- Irradiation Temozolomide For Primary Central Nervous System Lymphoma. RAC # 2081 049. N. Al Rajhi.
8. RTOG 0627 – Phase II trial of dasatinib in patients with recurrent glioblastoma multiforme. RAC # 2081 013. N. Al Rajhi.
9. 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 107. N. Al Rajhi.

10. RTOG 0631- Phase II/ III Study of Image – Guided Radiosurgery/SBRT for Localized Spine Metastasis, RAC # 2091 073. N. Al Rajhi.
11. RTOG 0724 – Phase III Randomized study of concurrent chemotherapy and pelvic radiation therapy with or without adjuvant chemotherapy in high risk patients with early stage cervical carcinoma following radical hysterectomy, RAC # 2091 078. N. Al Rajhi.
12. Prospective Data Collection of Newly Diagnosed Hodgkin's Disease and Non-Hodgkin's Lymphoma Cases. RAC # 2021 048. S. Akhtar.
13. Ewings RAC # 931 035. M. Memon.
14. Randomized Phase III trial of surgery alone or surgery plus preoperative Gemcitabine-Cisplatin in Clinical early stages (T2N0,T1-2N1,T3n) and (T3N1) Non-small cell lung cancer (NSCLC). RAC # 2031 059. Khalid Kattan, MD, K. Rehman, MD.
15. Positron Emission Tomography/Computerized Tomography in the Initial Staging of Locally Advanced Breast Carcinoma. T. Twegieri.
16. ALIMTA Study- A Randomized Phase II Study Comparing Pemetrexed Plus Best Supportive Care witn Best Supportive Care as Maintenance, Following First Line Treatment with Pemetrexed-Cisplatin in Patients with Advanced Non-Small Cell Lung Cancer. RAC # 2071 073. H. Husseini.
17. A Worldwide Observational Registry collecting Longitudinal data on the management of CML patients in routine practice. RAC # 2081 025. N. Chaudhri.
18. 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. Ahmed Al Zahrani.
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25. Establishment of Acute Lymphocytic Leukemia Data Base in the Department of Oncology. RAC # 2021 051. N. Chaudhri.
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28. (FACT-BMT) Functional Assessment of Cancer Therapy – Bone Marrow Transplant. RAC # 2071 079. A. Al-Zahrani.
29. Sarcoma Database. RAC # 2081 015. M. Memon.
30. A Pilot Trial of Pre-Operative Chemoradiotherapy using capecitabine (Xeloda), External Beam Radiation and Cetuximab (Erbitux®) Followed by Definitive Surgery in Patients with Localized (Non-Metastatic) Rectal Cancer. RAC # 2071 051. S. Bazarbashi.
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36. International Bone Marrow Transplant Registry (Autologous Transplant). M. Aljurf.
37. European Bone Marrow Transplant Registry. M. Aljurf.
38. 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). S. Akhtar
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50. Post –operative adjuvant chemotherapy followed by adjuvant Tamoxifen vs nil for patients with operable breast cancer (EORTC), RAC # 931 005. A. Ezzat.
51. Pre-operative Chemotherapy in Operable Breast Cancer (93-108), RAC # 931 006. A. Ezzat.
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ACADEMIC & RESEARCH DAY ABSTRACTS

Medical Oncology

Project Title: Extra Skeletal Ewing's Sarcoma Family of Tumors in Adults. Analysis of 57 Patients From Single Institution.

Investigators: *Amr El Weshi,MD, Ayman Allam, MD, Dahish Ajarim,MD, Fouad Al Dayel, MD, Rajeev Pant4, MD, Shouki Bazarbashi, MD, Muhammad Memon,MD*

Extra skeletal Ewing's Sarcoma (EES) is a rare form of soft tissue sarcoma. To assess the outcome and the prognosis of adult patients presenting with EES treated with multi-modality therapy, we reviewed all EES patients older that 15 years referred to our institution between January 1995 and December 2004. A total of 57 patients were identified. Their median age at diagnosis was 20 years (range, 15-570. The median size of primary tumor was 11 cm (range, 4-30 cm). Eighteen patients (31%) had metastatic disease at initial presentation. Wide surgical resection with negative margins was achieved in 23 (40 %) cases. Chemotherapy consisting of vincristine, adriamycin, ifosfamide, actinomycin-D was administered in 50 (88%) patients. Radiotherapy was delivered in 37 (65%) patients. Forty-one patients (72%) achieved complete remission and 16 (28%) progressed on therapy. Twenty-one (51%) patients relapsed. Local recurrence was encountered in 15 (36%) patients. At a median follow-up of 46 months (range 6-143 months), the 5-year event free survival (EFS) and overall survival (OS) rates were 35% and 47% respectively. Metastases at presentation, tumor size and surgical resection margin associated significantly with OS and EFS. EES is an aggressive type of tumor with high incidence of local recurrence and distant metastasis. This series showed that the outcome of adult EES is not unlike that of skeletal Ewing's sarcoma in terms of response to multi-modality treatment and the prognostic factors influencing treatment outcome. Adequate surgical resection, aggressive chemotherapy and adjuvant local radiation therapy, when indicated, constitute the optimal treatment to achieve the best results in this rare type of disease.

Project Title: ^{18}F-flourodeoxyglucose (FDG) Positron Emission Tomography (PET) Prior to High Dose Chemotherapy and Autologous Stem Cell Transplant Predicts Outcome After ASCT in Patients With Diffuse Large Cell Lymphoma and Hodgkin's Lymphoma. Results of 110 Patients.

Investigators: *S. Akhtar, A. Al-Sugair, M. Abuizaid, Y. Al Kadhi, M. Dingle, M. Abdelsalam, H. Soudy, A. Darwish, A. Altijani, M. Nabil, I.Maghfoor*

PURPOSE

There is emerging data indicating poor outcome in diffuse large cell lymphoma (DLCL) and Hodgkin's Lymphoma (HL) patients with positive ^{18}F-flourodeoxyglucose (FDG) positron emission tomography (PET) before high dose chemotherapy (HDC) and autologous stem cell transplant (ASCT). This study evaluates the impact of PET as a predictor of post HDC residua / progressive disease and relapse in patients with DLCL and HL undergone HDC ASCT.

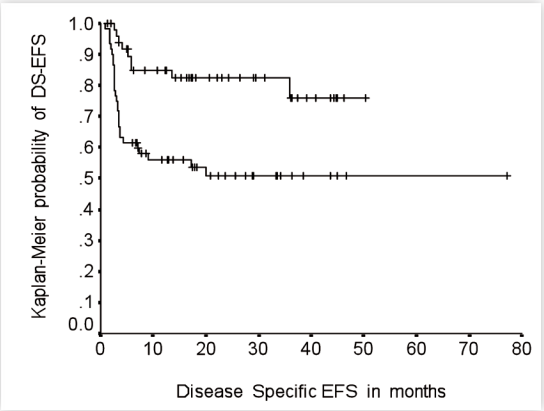
PATIENTS AND METHODS

From 2003 to May 2008, 162 consecutive patients with HL and DLCL underwent HDC ASCT. Of these, 110 patients had FDG-PET after salvage chemotherapy / prior to HDC ASCT. 53 patients were also enrolled in the prospective trial

of FDG-PET. ESHAP was used as salvage chemotherapy, responding DLCL or responding / stable HL patients had ESHAP as mobilization and BEAM as HDC. Patient had CT scan and FDG-PET before starting ESHAP, after 2-3 cycles of ESHAP / before HDC ASCT and 100 days post ASCT. FDG-PET, "positive study" was defined as study showing evidence of disease and "negative study" as no evidence of disease. Disease specific (DS) event is defined as presence of persistent disease, progression or relapsed disease after ASCT. DS event free survival (DS-EFS) was calculated from day 0. DS-EFS was calculated using Kaplan-Meier Method and comparison of the 2 groups (FDG-PET-Positive or negative) for event using chi-square method.

RESULTS

There were 66 (60%) male: female: 44 (40%), DLCL: 31 (28%) and HL: 79 (72%). Relapsed: 50 (45%), refractory 60 (55%). Median age at ASCT was 28 years (14 to 62). Median follow-up from ASCT is 20 months (1.2 to 77 months). Only 13 alive patients have <12 months of follow-up (2 of them already had an event). As of December 13, 2009, of these 110 patients, 37 (34%) had a disease specific (DS) event, DS event free survival (DS-EFS) is 66%. DS-EFS for PET negative vs. positive is 82% vs. 53% (P=0,002). Using Kaplan-Meier method, patients with a positive PET have 51% probability of DS-EFS vs. 76% for a patient with a negative PET scan at 77 months (P=0,0012). CT positive patient had DS-EFS probability of 62% vs. 51% for CT negative, (P=0,426).



CONCLUSION

Prior to HDC ASCT, positive PET scan indicates high risk of residual disease / progression or relapse. Many of these patients are likely to suffer from treatment failure. These patients are potential candidate for more aggressive and experimental therapies.

Disease Specific Event Free Survival (DS-EFS) Pre-HDC ASCT PET and CT

Results	Number	Event	DS-EFS %	P Value
PET-2 Negative	50	9 (18%)	82	0.002*
PET-2 Positive	60	28 (47 %)	53	
CT-2 Negative	26	7 (26 %)	73	0.407*
CT-2 Positive	84	30 (36 %)	64	

Project Title: The Role of Adjuvant Therapy in Women With Uterine Papillary Serous Cancer.

Investigators: *Mahmoud Abdelsalam, Alaa El Din Darwish, Hussein Soudy Hussein. Mohamed Ahmed, Amin Mohamed, Hamed Al Husseini*

BACKGROUND

Uterine papillary serous cancer (UPSC) represents only 10% of all uterine cancer and is associated with a significantly worse prognosis as compared with other histological types of endometrial cancer.

METHODS AND MATERIAL

This was retrospective study from February 1989 to January 2009.18 patients were reviewed who underwent definitive surgery followed by adjuvant therapy either platinum-based chemotherapy, radiotherapy, or both. Median age was 62 years (range 52 to 76). All patients were underwent total hysterectomy, salpingo-oopherectomy. Positive lymph nodes were found in 4 of 7 patients who underwent lymph node sampling/dissection. 7 patients had stage I/II, whereas 11 patients had stage III. 6 patients received chemotherapy, 5 patients received radiation therapy, while 7 patients received both chemotherapy and radiation therapy.

RESULT

Median follow-up was 17 months. The median survival and relapse-free survival was 33 months and 22 months, respectively. 9 patients were alive and free of disease of whom 5 patients were stage I/II and 4 patients were stage III. The most common site of relapse was distant. Early stage I/II and given radiation therapy were associated with significant improvement in relapse-free survival (P=0.004 for stage and P=0.007 for radiation therapy). Stage I/II only was associated with improvement in overall survival (P=0.05).

CONCLUSION

This study indicates that radiation therapy has role in management of UPSC by improvement relapse-free survival. Distant metastasis remains the major site of relapse. Future studies using combined modality therapy are needed to improve outcome in patient with UPSC.

Project Title: TP53 Mutations Predicts the Therapeutic Outcome of Breast Cancer Patients.

Investigators: *Taher Al- Tweigeri, Asma Tulbah, Abeer Al-Qassem, Mohammed Toulimat, Abdelmoneim M. Eldali, Adher Al Sayed, Usama Al malki, Adnan Ezzat, Mohamed Al Shabanah, Dahish Ajarim, and Abdelilah Aboussekhra*

PRELIMINARY RESULT

Breast Cancer has a major impact on the health of women worldwide. It is the most frequently diagnosed cancer and a leading cause of cancer-related death ranking first among Saudi females, with a frequency of more than 22% of all cancer types. Moreover, breast cancer in the Kingdom of Saudi appears relatively early in age and is highly aggressive. These features could be either environmental or genetic-related. The tumor suppressor TP53 gene is one of the most important genetic factors that play major roles in breast carcinogenesis. P53 is commonly altered in human cancer and the spectrum of p53 mutations in these cancers provides clues to the etiology and molecular pathogenesis of neoplasia. Indeed, several recent studies have shown the existence of association between certain p53 mutations and the response to therapy in breast cancer. Furthermore, p53 codon 72 genotype, which modulates the apoptotic capacity of p53, has been shown to predict the therapeutic response to chemotherapy in patients with various types of cancer.

We have performed direct sequencing of the p53 coding gene (through exons 4 to 9) in tissues from 104 breast cancer patients with a median age of 45 years, premenopausal 65%. The prevalence of TP53 mutations are around (40%). We studied the link between TP53 mutations and the codon 72 genotype and the pateints' response to therapy. We have found a significant association between TP53 mutations and 5 years disease free Survival and overall survival indicating that the patients that harbor normal p53 protein respond better to therapy and survive longer. On the other hand, no correlation has been found between the codon 72 genotype and the patients Disease free survival and overall survival.

CONCLUSION

Together, these results indicate that analysis of p53 mutations may provide a simple predictive biomarker for breast cancer therapy.

Project Title: ^{18}F-Flourodeoxyglucose Positron Emission Tomography (FDG PET) Response Predicts Survival in Primary Mediastinal Large B-Cell Lymphoma.

Investigators: *M. Abdelsalam, A. El Weshi, M. Abouzied, H. Hussaini, H.Soudy, A. Darawish, A. Altijani, I. Maghfoor, S. Akhtar*

BACKGROUND

Primary mediastinal B-cell lymphoma (PMBCL) is a distinct clinicopathological variant of large B-cell lymphoma. The optimal treatment is unknown, with some studies demonstrating favorable outcome compared to other types of diffuse large B-cell lymphoma. Role of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in this entity is not well reported.

AIMS

In this retrospective study, we evaluated the primary presentation, clinical characteristics, treatment outcome and impact of FDG PET on PMBCL management at our institution.

METHODS

All patients with PMBCL diagnosed and managed during 1995-2008 at our institution were identified from Oncology Data Unit. Patient's characteristics, prognostic factors, details of treatment and outcome were reviewed.

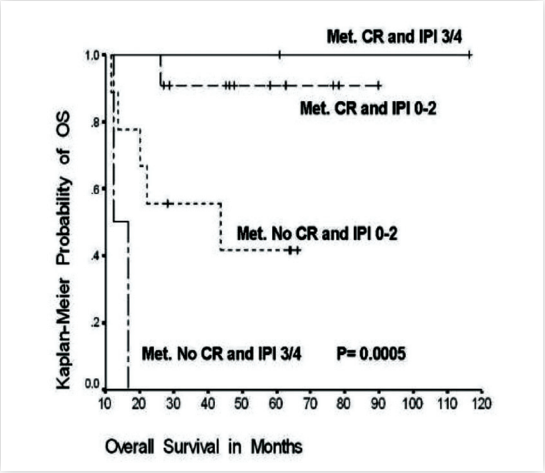
RESULT

Forty-seven patients were identified. Median age was 30 years (range 18-66). There were 26 (55%) females and 21 (45%) males. Forty-two patients (89%) had stage I-II disease. Seventeen patients (36%) had ECOG performance status of >2. Bulky disease in 37 (79%) patients. All patients received CHOP (with Rituximab in nine patients) chemotherapy followed by radiation therapy in 42 (89%) patients. Complete response rate + complete response unconfirmed was 76.6%. Median follow-up was 50.5 months and median overall survival (OS) and event free survival (EFS) were not reached. Univariate analysis showed female gender, early stages and response to treatment as good prognostic factors with higher OS and EFS, while response to planned treatment was the only factor that had impact on OS in multivariate analysis in all 47 patients. Twenty-five patients had FDG PET scan after chemotherapy. On Univariate analysis FDG PET negative patients showed significant improvement in OS and EFS compared to patients who were FDG PET positive; median OS and EFS were not reached in FDG PET negative patients and they were 22.2 and 5.9 months respectively in FDG PET positive patients (p=0.002 & 0.004 respectively).

On multivariate analysis, female gender (p=0.046) was the only significant factor among metabolic response (p=0.099), CT response (p=0.518), and age (p=0.231). Regardless of IPI score, patients with metabolic CR on FDG PET had an excellent OS (p=.0005) and EFS (p=0.0056) Figure attached (OS).

CONCLUSION

In conclusion, Female gender carries favorable prognosis in PMBCL as reported previously in the literature. More importantly, despite having small number of patients with FDG PET, our data supports that achieving metabolic CR on FDG PET leads to significant prolongation of OS & EFS. Metabolically negative FDG PET is stronger predictor of OS and EFS compared to IPI in PMBCL.



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The Department of

ORTHOPEDICS SURGERY

Orthopedics Surgery

CHAIRMAN

Zayed Al-Zayed, MD

The Orthopedic Surgery Department, through the Research Advisory Council, is exploring various measures to utilize resources available to strengthen our clinical practice by doing research and by publishing our data in international peer-reviewed journals, in order to measure outcomes, explore new methodologies of treatment, to standardize care and to acquire state of art technology. It is these publications that put our Department on the map. For example, we have submitted articles and manuscripts to the following Journals for publication:

- The Journal of Pediatric Orthopaedics - “The Vertical Expandable Prosthetic Titanium Rib Implant for the Treatment of Congenital and Neuromuscular Scoliosis KFSH&RC Experience”.
- The Journal of Children’s Orthopaedics - “Outcome of Contoured Iliac Crest Allograft Interposition in a Modified Pemberton Acetabuloplasty for Late Presenting Developmental Dislocation of the Hip: Technique and Short Term Results”.
- The Journal of Pediatric Orthopaedics B - “Clinical and Radiological Outcome of Shoulder Sequalae of Birth Brachial Plexus Palsy (A Retrospective review of 13 cases)”.

Our future goal is to intensify research activities of the Department as we believe that we have interesting pathologies in our service that warrant and deserve publication in international journals.

RESEARCH PROJECTS

Project Title: The Vertical Expandable Prosthetic Titanium Rib Implant for the Treatment of Congenital and Neuromuscular Scoliosis (KFSH&RC Experience)
RAC Project #: 2100006
Investigators: *Dr. Zayed Al-Zayed, Dr. Mohamed Samy, Hanan AlGhammas*

Project Description

A retrospective study review of the radiographs of 19 patients with congenital and neuromuscular scoliosis in King Faisal Specialist Hospital and Research Center (KFSH&RC,) which were treated by Vertical Expandable Prosthetic Titanium Rib (VEPTR), to evaluate the outcomes of VEPTR implant application on indirect scoliosis correction and space available to the lung at final encounter.

Progress

The patients significantly improved and maintenance scoliosis correction and the space available to the lung were increased in the last follow up with no evidence of spine growth disturbance with drop in chest infection attacks and low complication rate.

The space available for lung, comparing the ratio of the height of the concave lung to the convex lung improved from a mean of 80.53% preoperatively to 88.33% at follow up (see Table1).

Major finding

The VEPTR is a safe FDA approved device. This efficient method is providing control to the scoliosis, and allowing spine to grow as well as the lung underneath to expand in lung volume in children. We learned how to avoid the complications provided, and we stick to the proper indication.

Project Title: Outcome of Contoured Iliac Crest Allograft Interposition in a Modified Pemberton Acetabuloplasty for Late Presenting Developmental Dislocation of the Hip: Technique and Short Term Results.
RAC Project #: 2090134
Investigators: *Dr.William Wade, Dr. Thamer Al Hussainan, Dr. Zayed Al-Zayed , Dr. Nezar Hamdi, Dr. Dalal Bubshait*

Project Description

This is a retrospective study that reviews the radiographic results of the contoured iliac crest allograft interposition for pericapsular osteotomy in 147 late presenting developmental dislocation of the hip with a minimum follow up period of 2 years. The safety and the efficacy of this one stage treatment in achieving a reduced, stable hip with a corrected and maintained acetabular coverage was the main scope of this study.

Progress

The treatment protocol of a combined open reduction of the hip and pericapsular acetabuloplasty, inserting a contoured iliac crest allograft as interposition resulted in concentrically reduced and stable hips in 96.6% of our cases. The redislocation rate was 3.4 %. All the allografts were completely incorporated at 6 months post surgery with no graft related infections. In only 2 hips the acetabular correction was not maintained. None of the osteotomies required internal fixation for stability even in older children.

Major finding

We believe that a contoured iliac crest allograft as pericapsular acetabuloplasty interposition material renders excellent osteotomy stability that eliminates the need for internal fixation and -on the short term- maintains the correction of the acetabulum achieved intra operatively.

Table 1. The ratio of the height of the concave lung to the convex lung.

The Ratio	Median	Mean	Std Dev	Minimum	Maximum
The concave to convex ratio "Preoperative"	80.34	80.53	10.44	56.69	98.41
The concave to convex ratio "Follow-up"	89.55	88.33	8.32	73.68	100.00

Project Title: Clinical and Radiological Outcome of Shoulder Sequalae of Birth Brachial Plexus Palsy (A Retrospective Review of 13 Cases).
RAC Project #: 2091092
Investigators: *Dr. Nezar Hamdi, Dr. Dalal Bubshait, Dr. Mohammed Al-Shouli, Dr. Abdulaziz Al-Hajeri*

Project Description

This is a retrospective study that reviews all the cases of shoulder sequalae of BBPP with internal rotation contracture of the shoulder that underwent soft tissue procedures, to assess the preoperative abduction and external rotation of the shoulder, MRI/CT scan measurement of preoperative glenoid version, glenoid shape, and humeral head subluxation. Furthermore, to calculate the statistical significance with the post operative shoulder abduction, with active and passive external rotations.

Progress

There is a statistical significance between the preoperative abduction and postoperative abduction at 4 months and postoperative 1 year, and 2 years with p value of 0.001, 0.002, and 0.0016 respectively. And statistical significance found between preoperative external rotation and post operative external rotation at 4 months, 1 year and 2 years with p value of 0.008 , 0.008, and 0.004 respectively (see table 2).

Major finding: In conclusion, this retrospective study evaluates the short-term clinical results in a small series of patients and showed a relationship between the preoperative abduction of the shoulder and postoperative at 4 months, 1 year, and 2 years with a P value of 0.001, 0.002, and 0.0016 respectively. None of the 13 patients who had muscle release and tendon transfer worsened or failed to improve with surgery.

Table 2. The relationship between the preoperative abduction and post operative abduction.

	Pre op Abduction		Post op Abduction 2 years	
	Less than 90	More than 90	Less than 90	More than 90
Age < 6	7	1	1	7
Age > 6	5	0	1	4

The Department of

PATHOLOGY AND LABORATORY MEDICINE

Pathology and Laboratory Medicine

CHAIRMAN

Maher Albitar, MD

Project Title: KFSH Experience With Preimplantation Genetic Diagnosis (PGD) Petrospective Analysis.
RAC Project #: 2071076
Investigators: *Qubbaj, W., Awartani, K., Al-Rejjal, R., Al-Hassan, S., Al-Deery M., Coskun, S.*

Project Description, Progress, Major Findings

A retrospective study to review PGD cases performed at KFSHRC since 2001.

Single gene disorders: A total of 336 PGD cycles, for 203 patients were performed, testing for 66 different single gene disorders. Of those 248 cycles had embryo transfer, resulted in 123 pregnancies (36% per started cycles, 50% per transferred cycles and 51% of patients).

Chromosomal analysis: Preimplantation genetic screening (PGS) refers to techniques where embryos are screened for aneuploidies. It is usually performed by using fluorescence in-situ hybridization (FISH) technique. PGS was performed for patients with advanced maternal age (AMA), repeated implantation failure (RIF), and for those with repeated miscarriage (RM).

PGD using FISH technique was also performed for carriers of chromosomal structural abnormalities such as reciprocal or Robertsonian translocations, pericentric or paracentric inversions, in order to reduce spontaneous abortions and to increase the pregnancy rates.

Indication	Cycles	Embryo Transfer	Pregnancy (hCG+)
Aneuploidy	26	16	4 (25%)
Trisomy 21	10	7	2
Inversion	8	6	0
Turner	8	5	1
G6PD (X-linked)	2	2	0
Translocation (Reciprocal/Robertsonian)	50	27	12 (44.4%)
Hunter Syndrome (X-linked)	1	1	1
Fragile X (X-linked)	1	0	0
Total	**120**	**69**	**22**

Project Title: Preimplantation Genetic Diagnosis by Haplotyping (PGH) Using Whole Genome Amplification.
RAC Project #: 2081061
Investigators: *Qubbaj, W., Coskun S., Awartani K., Al-Rejjal R., Al-Hassan S., Al-Deery M., Al-Owain M., Al-Sayed M., Al-Hassnan Z., Banjar H., Bal-Obaid A., Qari A., Rahbeeni Z.*

Project Description, Progress, Major Findings

To develop a preimplantation genetic haplotype (PGH) strategy on MDA products from single cells (blastomeres). And to apply PGH for diseases with a known inheritance and identified genes, but the precise mutation causing the disease is unknown.

Fifty cycles were performed for 31 couples at risk of autosomal recessive or dominant, or X-linked disorders. A total of 328 embryos were tested, 301 of the samples were successfully amplified by MDA with an amplification efficiency of 92%. From the MDA product, 1462 PCR reaction were set and 47 (3.2%) amplification failure were observed. Allele drop out (ADO) were observed in 101 alleles (3.5%).

The confirmations of PGH results with the mutation testing were available for 269 embryos. Of those, 239 (89%) showed full concordance. There was a discrepancy between the PGH and mutation analysis from 12 embryos (4.5%). From the remaining, 4.5% were though concordant; PGH results showed a haploid pattern indicating that such embryos are being haploid or monosomic for that specific chromosome. Consequently, such embryos were not considered for transfer. There were 6 (2%) embryos on which diagnosis could not be predicted either due to maternal cell contamination or extensive ADO with PGH analysis.

For the cycles only PGH were performed either due to unknown mutation or gene expansion, there were 8 cycles for 4 couples. A total of 56 embryos were tested by PGH analysis and 53 (95%) give conclusive results to make a clear diagnosis.

Of the 50 cycles, 42 had embryo transfers resulting 15 pregnancies (35.7%) in 13 couples. One of the pregnancies resulted in abortion while the remaining is either ongoing or delivered.

Project Title: Whole Genome Amplification of Single Cells Using Different Amplification Strategies.
RAC Project #: 209 0013
Investigators: *Coskun S., Qubbaj, W.*

Project Description, Progress, Major Findings

Availability of different WGA methods and high ADO rate during PGD cycles require continuous evaluation of new developments. The aim of this study was to compare the two different MDA kits against the GenomePlex WGA method in a single cell.

Amplification efficiency and allele dropout rates on single lymphocytes and blastomeres following multiple displacement amplification for RepliG kit for 7 STR.

	Single Lymphocytes		Single Blastomeres	
STR Marker	*Amplification*	*ADO*	*Amplification*	*ADO*
D11S4160	25 (93%)	5 (10%)	20 (100%)	0 (0%)
D11S921	24 (89%)	3 (6%)	17 (85%)	0 (0%)
D11S902	25 (93%)	1 (2%)	20 (100%)	4 (10%)
D11S4130	24 (89%)	6 (13%)	20 (100%)	0 (0%)
D11S1888	23 (85%)	5 (11%)	20 (100%)	2 (5%)
D11S4096	25 (93%)	2 (4%)	18 (90%)	3 (8%)
D11S1307	26 (96%)	1 (2%)	20 (100%)	2 (5%)
Total	**172/189 (91%)**	**23/344 (7%)**	**135/140 (96%)**	**11/270 (4%)**

Project Title: Cell Free Fetal DNA (cffDNA) in Maternal Circulation: An Alternative Approach for Non-Invasive Prenatal Diagnosis
RAC Project #: 209 1001
Investigators: *Qubbaj, W., Coskun S., Tulbah M., Al-Kurdi W., Al-Hassan S., Al-Deery M., Al-Hassnan Z., Toulimat M.*

Project Description, Progress, Major Findings

To establish the non-invasive prenatal diagnoses (NIPD) strategy and to evaluate the reliability and the earliest detectable time during regular pregnancy follow up in addition to determining the benefits of such practice at KFSHRC patients.

During this period the QIA amp DNA Blood Mini Kit (Qiagen, Hilden, Germany) for cell free fetal DNA extraction was ordered and received. Blood was collected from 21 pregnant women underwent a PGD cycle and from IVF pregnant patients. Samples are kept frozen at -80C, analysis will start after 40 sample collection.

Project Title: Foxp3 Expression in Mycosis Fungoides: Immunophenotypical, Molecular and Clinical Study of 39 Cases. Single Institute Experience.
RAC #: 2091059
Primary Investigators: *Dr. Rami A. Al-Bugami, Dr. Abdulmonem Almutawa, Dr. Nasir Bakshi*
Co-Investigators: *Dr.Osamah T. Khojah, Mr. Abduraof Al-Agha, Mr. Mohammad Al-Ghamdi*

Project Description

39 cases of biopsy-proven mycosis fungoides (MF) were retrieved from the Department of Pathology & Laboratory Medicine (DPLM) archives from October 2002 till January 2009. Patient demographic & clinical data (age, sex, site, follow up), surgical pathology report, including Diagnosis & Immunohistochemistry Studies (IHC) and molecular study report of T-Cell Receptor (TCR) gene rearrangement have been collected. Foxp3 expression in the study group, will be evaluated by Immunohistochemistry studies (IHC).

The aims of this study are evaluation of the pattern of expression and distribution of Foxp3+ Treg cells in previously established cases of Mycosis Fungoides by Immunohistochemistry Studies (IHC), determining if the expression of Foxp3+ Treg cells has any prognostic significance in the context of the clinical behavior, and assessing the concordance between the Foxp3+ expression and T-cell receptor (TCR) gene rearrangement in Mycosis Fungoides.

Progress

- Data Collection (achieved)
- Evaluation of Foxp3 expression according to College of American Pathologist scoring system for nuclear staining (achieved)
- Tables and Figure (achieved)
- Statistical analysis of data (in progress)
- Manuscript writing and reviewing (in progress)

Project Title: Effect of HBV and HCV Chronic Infection on the Amplification of c-myc and Her-2/neu Protooncogenes and the Tumor Suppressor gene, p53, in HCC in Saudi Patients.
RAC Project #: 2060024
Primary Investigator: *Ahmed Al-Qahtani, PhD*
Co-Investigators: *Mohammed Al-Ahdal, PhD, Abdol-Monem Al-Ghamdi, MD, Hadeel Al-Manaa, MD, Magdy Aly, PhD*

Project Description

Amplification of the two oncogenes HER-2/neu and c-myc and deletion of the tumor suppressor gene p53 are frequently encountered in cancerous tissues. The purpose of this study was to use the fluorescence in situ hybridization (FISH) technique for the assessment of HER-2/neu and c-myc amplification and p53 deletion and to relate these molecular markers to clinical and pathological factors in Saudi patients with Hepatocellular carcinoma. The study was conducted on 40 paraffin-embedded tissue samples originally taken from either Hepatitis C Virus (HCV) or HBV-infected patients. Results revealed that the level of HER-2/neu, c-myc and p53 in the malignant group was significantly increased as compared to the control group. Of the 40 patients, 3 (7.5%) had amplification of HER-2/neu gene, 4 (10%) different patients had amplification of c-myc, and 26 patients (65%) had evidence of deletion of at least one allele on chromosome 17 for the p53 gene in a high proportion of cells.

There was a significant correlation between amplification of c-myc oncogene and the number of tumor masses. Moreover, significant correlation was observed between poorly differentiated tumors when compared with moderate or well differentiated tumors when c-myc was analyzed. On the other hand, c-myc failed to reveal any significant association between oncogene amplification and other clinicopathological variables examined. Univariate analysis revealed a strong association between deletion of p53 and multiple tumor mass ($p < 0.001$). No statistical correlation could be detected between deletion of p53 and tumor size, grade, stage and tumor differentiation.

No significant difference could be detected in the mean survival time of patients positive for the alteration of the genes compared to the patients who showed no alterations for the same genes. However, when the stage of the tumor was analyzed, there was a significant difference in the mean survival time between patients who showed gene alterations compared to patients with no changes in the studied genes.

When overall survival was analyzed, only patients with c-myc amplification had a lower median survival (20.75 months) than patients without c-myc amplification (35.82, $p = 0.009$). Genetic alterations of HER-2/neu and p53 genes had no effect on survival 2.

In conclusion, the combination of HER-2/neu, c-myc and p53 could be useful markers to stratify patients into different risk groups.

Progress:

Project completed and manuscript submitted (June 2010).

Project Title: A Study of FLT-3 and NPM-1 Mutation Status in Acute Leukemia in the Saudi Population-A Retrospective Analysis.
RAC Project #: 2081 062
Investigators: *AJ Saleh, TM Owaidah, SO Ahmed, SY Mohamed, A Al Serahi, H Al Zahrani, N Bakshi, MF Ul-Haque*

Project Description

To determine the prevalence of FLT-3 mutation (ITD and TKD) and NPM-1 in acute leukemia (Myeloid, Lymphoid and Biphotypic acute leukemia) in the Saudi population and to investigate the correlation between the presence of FLT3 mutation and outcomes (including CR rates, cumulative incidence of relaps (CIR), disease free survival (DFS) and overall survival (OS).

Progress

Active

Project Title: Evaluation of a New D-Dimer Test in Combination With Preset Clinical Probability Score for Diagnosis of Pulmonary Ambolism and Deep Venous Thrombosis.
RAC Project #: 2081 031
Investigators: *TM Owaidah, K Maghrabi, H Al Zahrani, A Al Sayed, M Moawad, M Zeitouni, N El Kum, F Skaff, R Naufal*

Project Description

The use of both pretest clinical probability scoring system and D-Dimer resulted in better decision making and early diagnosis of thrombosis. To study the hypothesis of implementation of D-Dimer measurement with the clinical pre test probability would help in detecting thrombosis in patients presenting to with clinical suspicion of thrombosis. To test the safety of withholding additional diagnostic testing and anticoagulation treatment in patients who have a negative D-Dimer and low probability at presentation. To measure the Negative Predictive Value (NPV) of using both preclinical score system and D-Dimer in exclusion of thrombosis in patients presenting with DVT/PE. To measure the Positive Predictive Value (PPV) of using both preclinical score system and D-Dimer in patients presenting with DVT/PE.

Progress

Active.

Project Title: Frequency of Factor V Leiden and Prothrombin Mutation in Tested Samples for Thrombophilia in KFSHRC-R and Concordance of Functional Tests for Activated Protein C Resistance and Molecular Tests for Factor V Leiden Mutation.
RAC Project #: 2091 056
Investigators: *A Al Shaikh, M Abdulaali, R Al-Nounou, TM Owaidah*

Project Description

The aim of this study is to estimate the laboratory based frequency of factor V leiden and prothrombin gene G20210A mutation and to study the concordance between functional assays and molecular studies for Factor V Leiden.

Progress

Active.

Project Title: The Significant of Phosphatidylserine as Predictor of Antiphospholipid Syndrome and Concordance With Other Antiphospholipid Antibodies.
RAC Project #: 2091 039
Investigators: *T Owaidah,O Khoja, M Al Kaff, T Al Shehri, H Khogeer*

Project Description

Antiphospholid Syndrome (APS) is immune medicated disease that is defined by clinical and laboratory criteria. Although there are many studies to define the Lab criteria. Although there are many studies to define the Lab criteria for the disease, but there is a new report about other APA that can be used for defining the disease. Here we are retrospectively analyzing the laboratory data for the two new APA that can be used as marker for APS.

Progress

Active.

Project Title: Molecular Hematology: The experience at KFSH&RC Over the Last 15 years.
RAC Project #: 2091 082
Investigators: *SH Khalil, R Al-Nounou, N Bakshi, TM Owaidah*

Project Description

To find the frequency of positive molecular assays within the Hematological malignancies. To estimate the correlation between the positive molecular test and other conventional laboratory assays. To calculate the sensitivity and specificity of each molecular tests within the Molecular Hematology Laboratory. To review all validation methods for Molecular Hematology Diagnostic tests.

Progress

Active.

Project Title: Molecular Genetics for Glanzmann Thrombasthenia at KFSH&RC.
RAC Project #: 2091 067
Investigators: *H. Masmali, T Owaidah, A Albanyan, A Almusa, M Saleh*

Project Description

Glanzmann Thrombasthenia (GT), an exceptional inherited platelet disorder is characterized by a complete lack of platelet aggregation due to a defect in the IIb IIIa complex or to a qualitative abnormality of this complex.

Advances in molecular biology have permitted to precise the molecular abnormality on aIIb or b3 genes responsible for the disease and have also contributed to a better knowledge of normal platelet physiology. This study will work on the issue of functional tests and molecular mutations for patient with GT will compare results with other published result.

Progress

Active.

Project Title: Chronic Myeloid Leukemia: Development and Validation of Therapeutic Hematoproteomic Biomarkers.
RAC Project #: 2050 040
Investigators: *TM Owaidah, M. Al-Jurf, A Alulia*

Project Description

This project will focus on the analysis of global protein expression profiles for patients with CML in the chronic phase (CP CML). We will analyze peripheral blood (plasma/serum) and bone marrow samples from the same patients 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 predict response to therapy or disease resistance. This information will help clinicians develop a customized treatment plan for each individual patient.

Progress

Active.

Project Title: Proteomics Approach to Biomarker Discovery in Aplastic Anemia.
RAC Project #: 2060 021
Investigators: *AA Alaiya, M Al-Jurf, M Al-Mohanna, H Al-Zahrani, TM Owaidah , F Al-Mohareb*

Project Description

This study will focus on the analysis of global protein expression profiles in patients diagnosed with AA, PNH and hypoplastic MDS in an effort to better our understanding of the inter relationship among these different bone marrow failure syndromes. We hope to characterize the differentially expressed proteins that are characteristic of these disease entities. The data generated will be used to aid in more objective differential diagnosis of these diseases and subsequently to identify and stratify subset of patients for appropriate treatment modalities.

Progress

Active.

Project Title: Development of Autologous Stem Cell Therapy for Patients With Severe Peripheral Arterial Disease of the Lower Limbs – A Phase Non-Randomized Study.
RAC Project #: 2081 021
Investigators: *C. Adra, H. Humaidan, S. Bassel, F. Al-Dayel, A. Alaiya, T. A. Rana, TM Owaidah, M. Al-Kaff*

Project Description

The primary aim of this study is to use autologous transplant of mononuclear cells derived from either bone marrow or peripheral blood from patients with severe

limb ischemia and to assess the efficacy, safety and feasibility of treatment protocol. The study in addition; aims to identify PAD–associated biomarkers using global protein expression analysis.

Progress

Active.

Project Title: Prevalence and incidence of Hemophilia A & B Inhibitors Among Hemophilic Patients in Saudi Arabia.
RAC Project #: 2081 077
Invesigators: *TM Owaidah, AK Al Moomen, H Al Zahrani, A Almusa, M Saleh, R Al-Nounou, F Al Manjomi, AS Al Omari, F Al Othman, F Al Qasim, A Trawah, F Batniji, M Ahmed, G Zaher, AH Al Abdullatif, A Al Dayel, H Al Saeed OA Al Nada, M Abou Riash*

Project Description

Hemophilia A is an X-linked disease that affects males at prevalence of 1:5000-10000 while the incidence of hemophilia B is 1:34,500 male. Although it is rarely observed, it can be very serious (life threatening) and costly disease for families and countries. The development of inhibitor, which usually results as a conscience of administration of blood product or manufactured factor, concentrate, is a relatively common problem. The prevalence of inhibitors for Hemophilia A range from 3.6-27% whereas for Hemophilia B risks very low 3-5%.

The objectives of this study are to screen for inhihibitor formation in both types of Hemophilia to estimate the prevalence rate after confirmation of the diagnosis and the risk factors for development of inhibitors. It will also look at the incidence rate for inhibitor formation overtime. The study will be conducted in two phases in Riyadh region followed by national screening using different diagnostic assays.

Project Title: Inhibitor Development in Previously Untreated Patients (PUPs) or Minimally Blood Component-Treated Patients (MBCTPs) when Exposed to von Willebrand Factor-Containing Factor VIII (VWF/FVIII) Concentrates and to Recombinant Factor VIII (rFVIII) Concentrates: an International, Multicentre, Prospective, Controlled, Randomized, Open Label, Clinical Trial. (SIPITT Study).
RAC Project #: 2091 055
Investigators: *TM Owaidah, M Saleh, A Almusa, H Al Zahrani, M Abu Riash, M Ashour*

Project Description

Inhibitor development is the most challenging complication of haemophilia treatment and the highest economic burden for a chronic disease. Treatment of haemophilia mainly based on replacement of the deficient factor. Two types of factor concentrates are available (Plasma derived and recombinant). It is important to know whether plasma-derived and recombinant products are associated with a different risk of inhibitor development in previously untreated patients (PUPs) or not. Unfortunately, no randomized clinical trials are available to provide the evidence we need.

The study is an international, multicenter, prospective, controlled, randomised, open-label clinical trial on inhibitor frequency in patients previously untreated (PUPs) or minimally blood component-treated (MBCTPs) when exposed to plasma-derived, von Willebrand factor-containing factor VIII (VWF/FVIII) concentrates or to recombinant factor VIII (rFVIII) concentrates.

The objectives is to assess the immunogenicity of VWF/FVIII and of rFVIII concentrates by determining the frequency of inhibitor development in PUPs and MBCTs in the first 50 EDs or in the first 3 years from enrolment, whichever comes first.

Progress

Active.

The Department of

PEDIATRICS

Pediatrics

The importance of clinical research is highly valued in the Department of Pediatrics. Advances in medicine is largely based on basic and clinical researches that are translated into practice. Clinical research is complementary to good clinical practice because it stimulates the creativity of the researchers, hones their skills, and provides local experiences. However, conducting research in our community is a challenge due to lack of funding, resources, and appropriate support.

This report summarizes the research activities of the Department of Pediatrics. Despite the fact that the majority of these studies were retrospective in nature, these represent the genuine motivation of our physicians towards conducting clinical studies and sharing their local experiences. Collaboration among our physicians and the scientists at the Research Centre has brought about excellent research studies as illustrated by some of our submitted projects.

The Department of Pediatrics is an advocate of research. We are periodically conducting our Pediatric Research Day, which is organized by our Pediatric Research Committee. We are working hard to continue to develop the research skills of our staff through educating and involving junior physicians in our research projects and encouraging them to attend research-oriented courses. In addition, major efforts to open a new venue for funding and support are being undertaken for new research ideas. We are confident that our multifaceted research-related ventures will bring about additional research mileage wherein innovative ideas and topics will easily thrive.

CHAIRMAN

Saleh Al Mofada, MD

RESEARCH ACTIVITIES

Project Title: Outcome after Renal Transplantation for Focal Segmental Glomerulosclerosis (FSGS) in Children.
RAC Project #: 2080042
Principal Investigator: *A Abdulaziz Alshehab, MD*
Co-Principal Investigator: *H Al Mojalli, MD*
Co-Investigators: *E Al Sabban, MD, I Al Hassoun, MD, A Al Abbad, MD*

Abstract

Background: Focal segmental glomerulosclerosis (FSGS) is the primary diagnosis resulting in end stage renal disease in approximately 12% of children receiving renal transplantation. Recurrence of FSGS after renal transplantation is a frequent and still unpredictable complication. However risk factors for recurrence have not yet been clearly identified.
Methods: It is a retrospective study, reviewed 15 pediatric patients who diagnosed as FSGS and received 16 renal allograft from January 1991 through December 2006 in one center.
Results: Recurrence of FSGS occurred in one recipient (6.6%). family history of FSGS was present in 60% of the patients and 5/7 (71%) of recipients had mesangial proliferation in the first biopsy of the original disease, native nephrectomy performed in one patient. Age at onset of original disease was less than 6 year in 73% of the recipients and duration of progression to ESRD was less than 3 year in 53% of the recipients, 10/15 of them was less than 12 year of age at the time of transplantation. ATN occurred in 53%of recipients and it was 100% in cadaver donor (CAD) and 12.5% in living related donor (LRD). Five year graft survival rate was 93.4% and it was 100% in LRD.
Conclusion: Recurrence of FSGS in renal transplantation is unpredictable and it is low in our population compared to international recurrence rate which can be explained by present of hereditary form of the disease in our patients. Clear risk factors for recurrence have not been identified. Efforts to elucidate the mechanism of recurrence and to delineate the risk factors based on genetics, potential circulating factors through multi-center controlled trial are required before we can assess outcome in renal transplantation for FSGS.

Project Title: Short-Term Outcome of Infants Less than 1500 Grams: Local Experience.
RAC Project #: 2071057
Investigators: *F Al Hazzani, S Al Aliyan, A Kattan, E Khadawardi*

Abstract

Objective: To describe and analyze the outcome of very-low-birth-weight infants admitted at our neonatal intensive care unit and compare the results to data published by the National Institute of Child Health and Development.
Methods and Design: Biodemographic data and multiple outcome measures were analyzed for infants with birth weight of less than1500 grams from January 2006 until January 2008 as part of the NICU database.
Results: A total of 186 infants with birth weights of 1500 g or less were recorded. Of these 186 infants, 154 (82.8 %) infants survived to discharge. Seventy six (40.9%) were male, mean gestational age (GA) was 29 ± 2.9 (Mean ± SD) weeks with a range of 21 weeks plus 6 days to 36weeks plus 2 days and mean birth weight was 1062 ± 302 (Mean ± SD) grams with a range of 420 to1495 respectively. Fifty seven (30.6%) infants were small for gestational age. Antenatal steroids were given to 74.2% of mothers. Eighty five percent of infants were born by Cesarean section. The rate of BPD, PDA, IVH, PVL, NEC, ROP and late onset sepsis were17.7%, 31.2%, 12.9%, 3.8%, 7.5%, 28.3% 21.9% respectively.
Conclusion: In this population of very low birthweight infants, survival rate and complications of prematurity were comparable to international data

Project Title: Allogenic HLA-Identical Bone Marrow Transplantation in Major Histocompatibility Complex Class II Deficiency: A Single Centre Experience.
RAC Project #: 2051049
Investigators: *H Al-Mousa, Z Al-Shammari, A Al-Ghonaium, H Al-Dhekri, S Al-Muhsen, B Al-Saud, R Arnaout, A Al-Seraihy, A Al-Jefri, A Al-Ahmari, M Ayas, H El-Solh*

Project Description, Progress, Major Findings

The main objective of this study is t o review KFSH&RC bone marrow transplantation experience for patients

with MHC Π deficien cy from 1993-2004 and focus on factors that might affect the outcome including: Patients characteristics (e.g.: age, sex, clinical presentation, preexisting infections, status pre-BMT, etc.), conditioning regimen, toxicity, engraftment, Graft Versus Host Disease (GVHD), immune reconstitution, survival rate, prognostic factor and comparison of our results to international data. Major Histocompatibility Complex Class II deficiency is a rare combined immunodeficiency disease. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment. Between June 1994 and February 2007, thirty children with MHC II deficiency underwent thirty three HSCT procedures. Median age at HSCT was 27 months. The sources of stem cells were unmanipulated bone marrow from HLA-identical related donors in 26 patients, one antigen-mismatched bone marrow in three patients and unrelated umbilical cord for one patient. Conditioning was with one of three myeloablative regimens: regimen A (18 patients): Busulfan (BU), Cyclophosphamide (CY) and Etopside (VP-16), regimen B (2 patients): BU, CY and anti-thymocyte globulins (ATG), regimen C (1 patient): CY, TBI (total body irradiation) or reduced intensity regimen (12 patients): fludarabine, melphalan and ATG. Median CD34 dose was 8.3 x 106/kg. Twenty patients immune reconstituted and had sustained engraftment that ranges from 9-100% for lymphoid and 5- 100% for myeloid lines. The overall disease-free survival rate was 66% and 76% post HLA-identical HSCT with a median follow-up of 6.3 years. In HLA-identical transplants reliable donor stem cell engraftment and immune reconstitution were achieved through myeloablative or reduced intensity conditioning. Further studies and long term follow up are required to determine the appropriate conditioning regimen.

Project Title: The Outcome of Hemopoietic Stem Cell Transplantation in Severe Combined Immunodeficiency Diseases: KFSHRC experience Compared to International Data .

RAC Project #: 2051052

Investigators: *S Al-Muhsen, M Ayas, N Al-Khamees, A Al-Ghonaium, H Al-Rayes, H Al-Mousa, H Al-Dhekri, R Arnaout, A Tbakhi, H El-Solh, A Al-Seraihy, A Al-Jefri, S Rifai, H Shahin*

Project Description, Progress, Major Findings

The aims of this study are to look at the outcome of hematopoietic stem cell transplantation in severe combined immune deficiency at KFSHRC by different measures: (1) survival; (2) immune constitution/engraftment; (3) HSCT-related complication; and to define the predictor of favorable outcome related to pre, during or post-transplant variables.

Transplantation of hematopoietic stem cells provide cure for severe combined immune deficiency (SCID) patients. Data on long-term outcome of this treatment in our area is limited. We report for the first time the long term survival after HSCT in SCID patients in Saudi Arabia.

108 transplants in 100 SCID patients have been performed between Jan 1993 to Dec 2006 at King Faisal Specialist Hospital, Riyadh, Saudi Arabia. 54% T-B- SCID. 13%T-B+ SCID, 13% ADA deficient SCID, 9%Omenn syndrome, 6%CD8 Lymphopenia, and 5% were unclassified with severe T cell dysfunction. Median age at HSCT was 7 months (range1-77 months). The source of stem cell was mainly un-manipulated marrow from genoidentical or phenoidentical donor (93%), unrelated matched umbilical cord (4%) and peripheral stem cell from matched related donor (3%). 46% were not conditioned, 25% received Busulphan 16mg/kg and cyclophosphamide 200mg/kg, 5% received additional ATG, 25% received cyclophosphamide only. GvHD prophylaxis consisted of cyclosporine (CSA) and methotrexate (MTX) in 35%, CSA alone in 45%, CSA and steroid in 3%, CSA and Mycophenolate Mofetil (MMF) in 2%, and no prophylaxis in 15%.

The overall survival at the time of analysis was 83% with reasonable engraftment as assessed by short tandem repeats for both lymphoid and myloid lineage. Patients with T-B+ had better prognosis than T-B-SCID (91% Vs 83% survival). On the other hand ADA deficiency had the worst outcome (71%). Transplant from HLA-genoidentical matched donor associated with the best outcome (89% survival). Patients received reduced intensity conditioning before stem cell transplantation had the most favorable outcome (95% survival), while non-conditioned patients had lower survival rate (83%). The worst prognosis as

expected for patients received myelo-ablation (70% survival). However, among those who survived; patients received myelo-ablative chemotherapy had more stable engraftment with improved myeloid lineage and more stable immune reconstitution even for humoral immunity. Immune reconstitution and chimeric studies will be shown.

Hematopoietic stem cell transplantation provides long-term cure and survival for SCID. Whenever available, genoidentical HLA matched donor is the best source for stem cells. Reduced intensity conditioning might be an option especially if it correlated with stable engraftment and long-term immune reconstitution. Further prospective long-term studies are required

Project Title: Allogenic HLA-Identical Bone Marrow Transplantation in Leukocyte Adhesion Defect I: A Single Center Study.

RAC Project #: 2051053

Investigators: *H Al-Dhekri, G Al-Ghannam, A Al-Ghonaium, H Al-Mousa, S Al-Muhsen, B Al-Saud, R Arnaout, A Al-Seraihy, A Al-Ahmari, A Al-Jefri, M Al-Mahr, M Ayas, H El Solh*

Project Description, Progress, Major Findings

Leukocyte adhesion deficiency type 1 (LAD-1) is a rare, autosomal, recessive immunodeficiency disorder that presents with delayed umbilical cord separation, omphalitis, impaired wound healing, recurrent infections of the skin and lungs, and leukocytosis. The severe phenotype is fatal unless hematopoietic stem cell transplantation (HSCT) is performed.

We retrospectively performed a data analysis of eleven patients who were diagnosed with LAD-1 and underwent hematopoietic stem cell transplantations (HSCT) over the past 19 years (1991-2009) in a tertiary care hospital in Riyadh. 7 patients received HSCT from HLA-matched related donor (MRD); 3 received HSCT from unrelated cord blood (UR-CB), and 1 patient received HSCT from a mismatched related donor (MMRD). 3 patients underwent a second HSCT because of primary or secondary graft failure. The median age at diagnosis was 4.7 months and 8.7 months at HSCT.

The conditioning regimen consisted of cyclophosphamide (CY) and busulphan (BU) for all patients. Antithymocyte immunoglobulin (ATG) was added to cord blood transplant recipients. The graft-versus-host-disease (GVHD) prophylaxis consisted of cyclosporine A (CsA) and methotrexate (MTx) for related donor recipients (8 patients) and CsA and prednisone for cord transplant recipients (3 patients).

The overall survival rate was 91% for all patients with a median follow up of 94 months (range, 15 – 223 months). The chimerism analysis showed mixed chimerism in all MRD recipients; two UR-CB recipients had mixed chimerism and one had full chimerism. Two patients from MRD and one UR-CB recipient remained disease-free with a low CD18 expression. One patient died after T-cell depletion during the second transplant from a mismatched brother. Only one patient had an acute grade 2 GVHD and none had chronic GVHD.

We conclude that LAD-1 transplanted from MRD has an excellent outcome with minimal GVHD complications. Mixed donor chimerism with low CD18 expression appeared satisfactory to prevent recurrent infection. UR-CB HSCT is encouraging with a good outcome and represents another alternative in the absence of MRD.

Project Title: Underlying molecular genetic defects of severe combined Immunodeficiencies (SCID) in Saudi Arabia.

RAC Project #: 2060012

Investigators: *H Al-Mousa, A Hawwari, O Alsmadi, A Al-Ghonaium, H Al-Dhekri, H Al-Rayes, S Al-Muhsen, R Arnaout, A Tbakhi, D Monies, S Wakil*

Project Description, Progress, Major Findings

Severe combined immunodeficiencies (SCID) represent the most severe form of primary immunodeficiencies. SCID is characterized by high level of genetic and clinical heterogeneity, as more than 10 conditions have been identified and can be distinguished according to cellular phenotype, inheritance pattern, and the responsible gene. The incidence of SCID in Saudi Arabia is not well established but an initial data suggested a 20 fold increase

relative to the international figure. This is mostly due to the high rate of consanguinity in the country (56%). Although the common phenotypes and genotypes of SCID are well established world-wide, little is known about SCID in Saudi population. In this report, we document for the first time, the SCID phenotypes and genotypes in Saudi patients.

Seventy eight SCID patients from 60 families who have been followed by the immunodeficiency clinics at King Faisal Specialist Hospital and Research Center (KFSHRC) were enrolled in th is study. All patients were divided in subgroups based on lymphocytes phenotypes then screened for mutations on the genes responsible for the phenotypes. T-B-NK+ SCIDs were screened for RAG 1/2, Artemis and LIG4 mutations. T-B+NK- were screened for γc and JAK3 mutations. T-B+NK+ were screened for IL7RA mutations. T-B-NK- SCIDs were screened for ADA and PNP mutations. SCIDs with Omenn phenotype were screened for RAG1/2 and Artemis defects while patients with CD8 deficiency were screened for ZAP70 defects.

Autosomal mode of inheritance is predominant in Saudi SCIDs patients. T-B-NK+ represent the commonest phenotype (35%) followed by T-B-NK- (14%). Novel and common mutations in RAG1, RAG2 and Artemis are responsible for 82% of T-B-NK+ SCID while novel and c ommon mutations in ADA and PNP are responsible for T-B-NK- phenotype. All T-B+NK- SCID are caused by novel JAK3 defects. IL7Ra mutation is responsible for only small fraction of T-B+NK+ phenotype. Five out of nine patients with Omenn syndrome had novel hypomorphic mutations on RAG1/2. Novel ZAP70 mutations are responsible for 3 out of 5 CD8 deficient SCIDS. Artemis and RAG1 defects are responsible for only 3 out of 14 patients with leaky SCID. Autosomal recessive mode of inheritance is mainly responsible for SCID in Saudi Arabia due the high rate of consanguinity. T-B-NK+ is the commonest phenotype. Twenty six patients (33%) lack a known genetic etiology and are likely to carry mutations in the regulatory elements in the SCID-causing genes or in novel genes that are yet to be discovered in Saudi population. Our efforts are underway to investigate this possibility by applying the whole genome scans on these cases via the use of Affymetrix high density DNA SNP chips in addition to homozygosity mapping.

Project Title: Underlying Molecular Defects of Chronic Granulomatous Diseases (CGD) in a Cohort of Saudi Patients.

RAC Project #: 2070017

Investigators: *S Al-Muhsen, O Alsmadi, A Al-Ghonaium, H Al-Mousa, H Al-Dhekri, S Al-Gazlan, H Al-Rayes, R Arnaout, B Al-Saud, A Al-Azami*

Project Description, Progress, Major Findings

Chronic granulomatous disease (CGD) is a primary immunodeficiency caused by genetic defect in one of the components of NADPH oxidase of the phagocytic cells. This system is important in combating catalase producing organisms such as many bacteria and fungi. In addition to susceptibility to infections, CGD patients are prone to non-infectious complications, as lymphadenopathy, hepatosplenomegaly, eczema, glomerulonephritis, and granulomatous colitis. The diagnosis of CGD is based on a compatible clinical presentation and demonstration of a defective respiratory burst. Several methods detect the production of reactive oxidants such as nitroblue tetrazolium (NBT) and dihydrorhodamine 123 oxidative burst assay using flowcytometry (DHR). With limitation in these diagnostic methods, there is clear indication to confirm the diagnosis by molecular genetics through demonstration of specific genetic mutations in one of the structural components of NADPH oxidase which is routinely done world wide.

There are four genetic mutations involving the phagocytic oxidase system that has been identified to date. The most common is an XL-recessive defect in gP91phox. Three other forms caused by AR defect in the other components of the NADPH oxidase system, encoding P22phox, P47phox, and P67phox respectively.(5-10) Recent data from a large national US registry indicated the XL-recessive form tend to present earlier and follow more severe course.

As per previous RAC approved project, more than 40 patients are followed for chronic granulomatous disease in the immunology clinic at King Faisal Specialist Hospital & Research 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.

Project Title: Underlying Molecular Genetic Defects of Primary Immunodeficiency Diseases in Saudi Arabia.
RAC Project #: 2080025
Investigators: *H Al-Mousa, A Hawwari, O Alsmadi, A Al-Ghonaium, H Al-Dhekri, S Al-Muhsen, B Al-Saud, R Arnaout, M El-Khalifa, D Monies, M Al-Hamed*

Project Description, Progress, Major Findings

There are wide varieties of primary immunodeficiency diseases (PIDs) that are caused by congenital defects of the immune system. Today, over 100 inherited PIDs are known to exist, with an incidence estimate of 1 in 10,000 to 1 in 2000 among live births. These include X-linked agammaglobulinemia (Bruton's Disease), common variable immune deficiency (CVID), selective IgA deficiency, and severe combined immune deficiency (SCID). PIDs result from defects in T-, B-, NK-, phagocytic cells or the complement system. Certain PID types like CVID and selective IgA deficiency are not always familial; their cause is unknown but the interaction of genetic and environmental factors may play a role in their causation. If untreated, PIDs may associate with frequent life-threatening infections and debilitating illnesses. The genes responsible for most of these diseases have been identified due to modern advances in molecular diagnostics, which enabled early disease detection and adequate treatment. Mutation detection approaches are available to identify mutations through genotyping and direct sequencing. As would be expected, the incidence of these disorders in Saudi Arabia is higher than the world overall rates due to high consanguinity, and there is a need to delineate the molecular bases underlying them. Based on our experience with the RAC-approved SCID project, it is anticipated that novel gene mutations and novel loci/genes that are unique to the Saudi population will be discovered. Results roots out from these studies will benefit patients and their families in terms of counseling, disease prevention through pre-implantation genetic diagnosis and prenatal diagnosis.

Project Title: Investigating the Role of Cellular Inhibitory Proteins in Eosinophils Apoptosis: Implication in Asthma/Atopy.
RAC Project #: 2080026
Investigators: *B Al-Saud, C Adra*

Project Description, Progress, Major Findings

Hypotheses: C-FLIP may have a role in the delayed eosinophils apoptosis phenomenon known in patients with allergy and/or asthma.
Objectives: To determine the role of c-FLIP in the regulation of eosinophils in allergic individuals by comparing them to healthy volunteers.
Methods: After an informed consent blood sample will be drawn from subjects, and purification of human blood eosinophils will be done using negative selection and immunomagnetic beads. To determine the magnitude of expression for c-FLIP at the protein and the mRNA level in eosinophils, an immunoblot analysis and RT PCR respectively will be done. These experiments will be done in the presence as well as in the absence of appropriate stimulations.
Significance: It is necessary to further understand eosinophil apoptosis mechanisms in health and in disease. This will be done by determining the role of c-FLIP. C-FLIP dysregulation association with human diseases has been recently reported, and the possibility of using c-FLIP as a therapeutic target is addressed in cancer and autoimmune diseases.

Project Title: Establishment of Primary Immunodeficiency Disease (PID) Registry at KFSHRC.
RAC Project #: 2081111
Investigators: *B Al-Saud, S Al-Muhsen, A Al-Ghonaium, H Al-Mousa, H Al-Dhekri, H Al-Rayes, R Arnaout, S Al-Gazlan, N Elsayed*

Project Description, Progress, Major Findings

PID registries from countries around the world have shown wide geographical and racial variations in the prevalence and pattern of PID. These registries helped in determining the frequency and the natural history of PID in these countries. Moreover, a registry can significantly improve research in the field of PID by collecting data over time and by connecting centers nationally and even internationally.

The rationale behind the establishment of the PID Registry is to determine the magnitude and types of PID disease encountered by our population at KFSH&RC. Upon successful data collection, other health care centres in Riyadh and subsequently across the country will be added to have a national representation of the registry.

Project Title: Cytomegalovirus Infections in Pediatric Unrelated Cord Bolld Transplantation, A Hospital Based Study.
RAC Project #: 2081063
Investigators: *S Al Hajjar, MD, A Al Seraihi, MD, I Manei, MD, A Al Ahmari, MD, M Al Ayas, MD, A Al Jefry, MD, S Al Muhsen, MD, H El Solh, MD, MM Shoukri, MD*

Background: Data regarding the risk factors and outcome for CMV infection following UCBT for pediatric patients are scant despite the fact that these grafts are increasingly used in children.
Methods: To determine the incidence, risk factors, and outcome for CMV infection, we performed retrospective review and case control study for 73 pediatric patients who received UCBT between January 2003 and December 2007.
Results: The overall incidence of CMV infection, early and late CMV infection was 58.9% (43/73), 62.8% (27/43) and 37.2% (16/43) respectively. Early CMV infection was treated with Ganciclovir Pre-emptive therapy that produced 76.9% success rate. Six of the twenty seven (22%) patients with early CMV infection progress to develop CMV end-organ disease including pneumonitis and retinitis. Disease progression was associated with high CMV antigenemia (≥70pp65^{+}PMNs) (p=0.237).
Significant risk factors for CMV infection included: recipient CMV seropositivity (p= <0.001), acute graft-versus-host disease (p=<0.001), steroid therapy (p=<0.001) and malignancy as underlying disease (p=<0.001). Recipient gender was not a risk factor for CMV infection but association was occurred with older age (p=0.002). Late CMV infection was strongly associated with previous history of early CMV infection (p=<0.001).

Conclusion: The overall incidence of CMV infection in children receiving UCBT in our center is 58.9%. We have identified a number of significant risk factors for early CMV infection following UCBT in pediatric age. Late CMV infection is associated with previous history of early CMV infection. Accordingly, extended surveillance of CMV antigenemia is recommended for patients who have previous history of CMV infection.

Project Title: Autoimmune Polyglandular Syndrome Type 1 in Saudi Children.
RAC Project #: 2091087
Investigator: *BS Bin-Abbas, MD, FAAP, FACE*

Project Description

Autoimmune polyglandular syndrome type 1 (APS-1) is a rare autosomal recessive disease. It is characterized by the presence of at least two of the three major components; hypoparathyroidism, candidiasis and adrenal insufficiency. APS-1 was previously described in several ethnic groups; however its clinical and biochemical features were not reported in details in Saudi children.

Objective: To describe the clinical, biochemical and immunological manifestations of APS-1 in Saudi population.
Methods: The medical files of seven consanguineous Saudi families with 20 affected siblings were retrospectively reviewed. They were followed at The Pediatric Endocrinology Clinic, King Faisal Specialist Hospital and Research Center for a mean duration of 6 years (January 1, 2000 to December 1, 2009). The age of the affected children ranged from 2 to 17 years. The included patients had at least 2 out of the 3 major clinical diagnostic criteria of APS-1.
Results: Fourteen children had neonatal chronic *mucocutaneous candidiasis* affecting nails and mouth. The most commonly presenting endocrine disease among

APS-1 patients was hypoparathyroidism. Eight patients had autoimmune Addison's disease. Hypothyroidism was diagnosed in 3 patients and 9 patients had alopecia universalis. Other endocrine and autoimmune disorders were infrequently seen including type 1 diabetes, growth hormone deficiency, celiac disease, autoimmune hepatitis and keratoconjuctivitis.

Conclusion: APS-1, although it is a relatively uncommon disorder in Saudi children, it affects multiple endocrine glands and associated with several autoimmune diseases where *alopecia universalis* is a common finding.

Project Title: Down Syndrome (DS) and Pulmonary Hypertension (PHT): The Experience at KFSH&RC.
RAC Project #: 2081119
Investigator: *H Banjar, MD, FRCPC*

Introduction and Objectives: Children with Down syndrome (DS) have an increased risk for developing pulmonary hypertension due to multiple factors. The objective of this study is: To identify the contributory factors that caused PHT in patients with DS and to identify the effects of the different medical and surgical interventions that have been offered to such patients and their out comes.

Methods: Retrospective chart review for all DS patients (Pts) referred to pulmonary service at KFSHRC-Riyadh for respiratory evaluation due to cough, recurrent chest infection and cyanosis during the period 1993-Dec 2008. PHT was defined as pulmonary artery pressure (PAP) on cardiac catheterization and or Echo studies to be > 50% of systolic systemic pressure. Demographic, clinical, diagnostic, morbidity and mortality data were collected.

Results: A total of 59 pts with DS, 34 (57.6%) Male, 25 (42.3%) female. 7 pts (12%) were premature. 39 (66%) pts are alive, 14 (24%) died, and 6 (10%) are lost follow up (FU). Age at diagnosis was 3.3 ± 3.9 yrs. Age at FU 9 ± 5.9 yrs. 46 pts (78%) had cardiac defects: 18 (39%) as common AV canal, 16 (35%) ASD, 8 (17%) VSD, 3 (7%) had PDA and 21 (46%) had multiple defects. 35/ 46 pts (76%) required cardiac repair at age of 2.6 ± 3.9 yrs. 44/ 59 (75%) Pts had PHT at diagnosis at Age of 3.2 ± 4 yrs, 13 (22%) mild type, 12 pts (20%) moderate, 19 pts (33%) had severe PHT. 10 pts, their PHT progressed, 9 remained within the same degree. 33 (56%) pts of the total DS group continued to have PHT at FU. One patient with AV canal and PDA developed Eisenmenger's syndrome and improved on Bosentan (from Functional "FC" IV → II) and 6 minute walk test from 30% → 75 % after 6 months of treatment. Another patient with ASD, VSD, Asthma and Obesity with FC III, improved on Bosentan to FC II. 3 pts with post repair of common A-V canal improved on Sildenafil. 28 (47%) pts had signs and symptoms with obstructive sleep apnea (OSA), 20 pts required Tonsilectomy and adenoidectomy and 4 required Trachesostomy to improve their respiratory symptoms. 45 pts (76%) were treated for asthma symptoms, and 35 (59%) Pts for chest infection. 41 pts (69%) required home O2 during their FU. 26 (44%) pts had radiological signs of gatroesophageal reflux(GER), 12 (20%) of them required Nissen fundoplication. 7 pts (12%) had celiac disease, 23 pts (39%) had hypothyroidism that required treatments. 20 pts (34%) had neurological problem as cerebral palsy and Seizures. 41 (69%) had other associated disease as skin, and eye problems. It was found that DS pts with cardiac defects were more prone to develop PHT and OSA than those who do not have cardiac defects (P= 0.05). Chest infection was more common in DS patients with PHT compared to those DS without PHT.

Conclusion: PHT is common in DS pts with or without cardiac defects. Physician should be aware of other factors that may cause PHT such as: OSA, asthma and GER. Vasodilators may have a favourable effect in DS with un-repaired cardiac defects. Furhter studies are needed to define the role of vasodilators in DS with PHT.

The Department of

PEDIATRIC HEMATOLOGY/ONCOLOGY

Pediatric Hematology/ Oncology

CHAIRMAN

Kwesi Sackey, MD

CLINICAL RESEARCH

The Central Data Unit (CDU) has stopped routine collection of retrospective data; RAC-Approved studies will however be supported by the CDU. PI's are being encouraged to obtain grant-support for collection of retrospective data or collect the data themselves. Collection of prospective data is progressing well. 5 New clinical research studies were approved by RAC in 2009.

ABSTRACTS/PRESENTATIONS (ORAL&POSTER)/MANUSCRIPTS

In 2009 the Department had 12 abstracts and presentations (both oral and poster) and 9 full-length manuscripts published. This is an improvement compared to the previous 5 years. Authors of manuscripts are encouraged to first submit them to PAGES (Publications Advisory Group for Excellence in Scientific papers), a Department group available to help enhance the quality of manuscripts before submission.

LABORATORY RESEARCH

The Department continues to collaborate with the Research Center at KFNCCC in Translational Research.

DEPARTMENT RESEARCH COMMITTEE

This committee continues to critically scrutinize the scientific & research merits of new proposals before submission to ORA.

RESEARCH INFORMATION EXCHANGE

In order to continuously update members of the department on Research Activities in the department there are two for the "CDU Minute" at each Department Meeting and the Research Activities Meeting (RAM) held quarterly. The latter also acts as a platform for presentation of Research in the Concept Phase.

RESEARCH ACTIVITIES

Project Title: Retrospective Review of Pediatric Patients Diagnosed with CML and Treated at KFSH&RC with Imatinib Mesylate.
RAC Project #: 2081084
Co-Principal Investigators: *Asim Belgaumi and Ali Al-Shehri*
Co-Investigators: *Hassan El-Solh, Mohammad Al-Mahr, Mouhab Ayas, Mahasen Saleh, Amal Al-Seraihy, Ali Al-Ahmari, Abdulrahman Al-Musa*

Project Description

As per title.

Project Title: Underlying Genetics of Familial Hemophagocytic Lymphohistiocytosis (FLH) in Saudi Arabia.
RAC Project #: 2080041
Co-Principal Investigators: *Ali Al-Ahmari and Osama Alsmadi*
Co-Investigators: *Ibrahim Al-Fawaz, Mouhab Ayas and Bandar Al-Saud*

Project Description

As per title.

Project Title: Allogeneic Transplant Using Reduced Intensity Conditioning: A Pilot Study.
RAC Project #: 2081053
Co-Principal Investigators: *Mouhab Ayas*
Co-Investigators: *Abdlh Al-Jefri, Amal Al-Seraihy, Ali Al-Ahmari, Mohammad Al-Mahr, Ashraf Khairy, Samer Markiz, Ibrahim Al-Hassan and Hassan El-Solh*

Project Description

As per title.

Project Title: Cardiac Iron Overload and Efficacy of Deferasirox (Exjade) on Patients on Chronic Blood Transfusion Secondary to Hereditary Blood Disorders, KFSH&RC.
RAC Project #: 2081106
Principal Investigator: *Abdlh Al-Jefri*
Co-Investigators: *Kwesi Sackey, Rajeh Sabah, Mahasen Saleh, Rubina Jamil Malik, Rajeev Sathiapalan, Nicy Joseph, Mohammad Salim, Fahad Al-Moharib, Yusuf Alkadh, Mahmoud Abu-Riyash and Mohammad Al-Ghamdi*

Project Description

As per title.

Project Title: Real Time PCR Assay of TdT for Detection of ALL in Cerebrospinal Fluid.
RAC Project #: 2090012
Principal Investigator: *Asim Belgaumi*
Co-Investigators: *Shahab Khan, Rong Bu, Azhar Hussein, Mohd Al Mahr*

Project Description

As per title.

Project Title: Metabolic Syndrome Prevalance Among Children With ALL After the End of Treatment.
RAC Project #: 2091043
Principal Investigators: *Abdullah Al-Nasser*
Co-Investigators: *Yasmin AlTwaijry, Abdulaziz Al-Sugair, Fahad Al-Dhafiri, Hanan Al-Mutairy, Almutaz Banifawaz*

Project Description

As per title.

Project Title: International Pediatric Fungal Network Registry.
RAC Project #: 2091044
Investigators: *Ibrahim Bin Hussein and Asim Belgaumi*

Project Description

As per title.

Project Title: Inhibitor Development in Previously Untreated Patients or Minimally Blood Component Treated Patients When Exposed to Plasma Derived von

Willebram Factor Containing Factor VIII Concentrates and to Recombinant Factor VIII Concentrates: An Independent International Multi-Centre Prospective Controlled Trial.
RAC Project #: 2091055
Investigators: *Tarik Owaidah, Mahasen Saleh and Abdulrahman Al-Musa*

Project Description

As per title.

Project Title: Second Allogeneic SCT in Pediatric Patients at KFSH&RC.
RAC Project #: 2081098
Principal Investigator: *Mouhab Ayas*
Investigators: *Abdlh Al-Jefri, Amal Al-Sheraihy, Ali Al-Ahmari, Mohd Al-Mahr, Asraf Radwan, Samir Markiz, Hassan El-Solh*

Project Description

As per title.

Project Title: Epidemiological, Clinical, Laboratory and Molecular Genetic Characterization of Childhood ALL in the Mid East and their Correlation With Induction Toxicity and Outcome: A Prospective Multi-Institutional International Collaborative Study.
RAC Project #: 2081108
Principal Investigator: *Abdlah Al-Nasser*
Co-Investigator: *Asim Belgaumi*

Project Description

As per title.

Project Title: Allogeneic Bone Marrow Transplant in Children With Myelodysplastic Syndrome: KFSH&RC Experience.
RAC Project #: 2081046
Investigator: *Amal Al-Sheraihy*

Project Description

As per title.

Project Title: Children With Low-Grade Gliomas: Experience of KFSH&RC.
RAC Project #: 2081035
Principal Investigator: *Amani Al-Kofide*
Co-Investigators: *Esam Al-Shail, Maher Hassounah, Mouhab Ayas, Ashraf Alrawashdeh, Yasser Khafaga, Hamoud Al-Mousa, Hind Al-Hindi, Fahad Al-Mohaileb*

Project Description

As per title.

Project Title: Allogeneic Stem Cell Transplant for JMML: Single Institution Experience.
RAC Project #: 2071048
Principal Investigator: *Ali Al-Ahmari and Othman Mosleh*
Co-Investigators: *Mouhab Ayas, Ibrahim Hassan, Abdullah Al-Jefri, Amal Al-Sheraihy, Mohd Al-Mahr, Samira Rifai, Ashraf Radwan, Samir Markiz, Hassan El-Solh*

Project Description

As per title.

Project Title: Allogeneic Stem Cell Transplantation in Patients With Fanconi Anemia Using Further Reduced Doses of Cyclophosphamide With Addition of Fludarabine.
RAC Project #: 2071037
Principal Investigator: *Mouhab Ayas*
Co-Investigators: *Ali Al-Ahmari Abdullah Al-Jefri, Amal AL-Sheraihy, Mohammad Al-Mahr, Samira Rifai, Ashraf Radwan, Samir Markiz, Hassan El-Solh*

Project Description

As per title.

Project Title: Where Do We Stand With Chronic Immune Thrombocytophenia in Children? A KFSH&RC Riyadh Experience.
RAC Project #: 2071012
Principal Investigator: *Rajeev Sathiapalan*
Co-Investigators: *Abdullah Al-Jefri, Abdulrahman Al-Musa, Mahasen Saleh, Amal Al-Sheraihy, Rajeh Sabbah, Nicy Joseph, Rubina Jamil Malik, Arlene Maculangan, Pranesh Kumar*

Project Description

As per title.

Project Title: Chemoreduction in Retinoblastoma.
RAC Project #: 2061040
Principal Investigator: *Amani Al-Kofide*
Co-Investigators: *Saleh Mesfer, Khawar Siddiqui, Gamal El Din Hassan Mohammed, Yasser Khafaga, Ashraf Alrawashdeh*

Project Description

As per title.

Project Title: Allogeneic Stem Cell Transplantation in Patients With Fanconi Anemia: The KFSH&RC Experience.
RAC Project #: 2061037
Principal Investigator: *Mouhab Ayas*
Co-Investigators: *Mohammad Al-Mahr, Abdullah Al-Jefri, Samira Rifai, Amal Al-Sheraihy, Ashraf Khary, Hassan El-Solh*

Project Description

As per title.

Project Title: Retrospective Review of Pediatric Ewing's Sarcoma (ES) and Primitive Neuroectodermal Tumor (PNET) Treated With POG CCG at KFSH&RC 1995-2004.
RAC Project #: 2051015
Principal Investigator: *Ibrahim Al-Fawaz*
Co-Investigators: *Mouhab Ayas, Samira Rifai, Christopher Alviedo, Yasser Khafaga, Zakaria Habib, Mohammed Al-Shabannah, Leifan Al-Otaibi, Abdulmoneim Eldali*

Project Description

As per title.

Project Title: Prospective Evaluation of Risk-Adapted Therapy for Patients With Non-Lymphoblastic Non-Hodkins Lymphoma.
RAC Project #: 2051018
Principal Investigator: *Asim Belgaumi*
Co-Investigators: *Amani Al-Kofide, Rajeh Sabbah Iqbal, Yasser Khafaga, Ravichandran Khandsamary, Walid Ali Mourad, Khawar Siddiqui, Mohammed Anwaruddin, Layla Osman, Qassim Al-Harbi, Ashraf Alrawashdeh*

Project Description

As per title.

Project Title: Retrospective Review of Pediatric Neuroblastom Treated at KFSH&RC 1975-2004.
RAC Project #: 2051032
Principal Investigator: *Ibrahim Al-Fawaz and Samira Rifai*
Co-Investigators: *Christopher Alviedo, Mouhab Ayas, Samir Markiz, Kawther Salamah, Yasser Khafaga, Zakaria Habib, Taghreed Salman, Othman Mosleh*

Project Description

As per title.

Project Title: Immune Reconstitution in Pediatric Patients Undergoing Allogeneic and Autologous SCT: A Single Institution Experience at KFSH&RC.
RAC Project #: 2051005
Principal Investigators: *Mouhab Ayas*

Project Description

As per title.

Project Title: GVHD in SCT Cases.
RAC Project #: 2051008
Principal Investigators: *Ashraf Radwan and Mouhab Ayas*

Project Description

As per title.

Project Title: Treatment of Infentile Acute Leukemia With High-Dose Chemotherapy Followed by HLA Matched Stem Cell Transplantation.

RAC Project #: 2041045
Principal Investigators: *Mouhab Ayas and Ashraf Radwan*
Co-Investigators: *Amal Al-Sheraihy, Abdlah Al-Jefri, Samira Rifai, Hassan El-Solh, Mohammad Al Mahr, A. Iqbal*

Project Description

As per title.

Project Title: Feasability of GCSF Stimulating Bone Marrow From Pediatric Donors as Stem Cell Source for Allo BMT.
RAC Project #: 2041031
Principal Investigators: *Mouhab Ayas*

Project Description

As per title.

Project Title: An Open-Label Multi-Centre Trial on Efficacy and Safety of Long Term Treatment With ICL 670 (10-20 Mg/Kg/Day) in Beta Thalassemia Patients With Transfusional Hemosiderosis.
RAC Project #: 2041038
Principal Investigators: *Abdlh Al-Jefri, F. Al-Mohareb, Y. Al-Kadhi*

Project Description

As per title.

Project Title: Retrospective Review of Pediatric Patients Diagnosed With Hodgkin's Lymphoma Treated at KFSH&RC.
RAC Project #: 2041046
Principal Investigators: *Asim Belgaumi, Rajeh Sabbah, Khawla S. Al-Kuraya*
Co-Investigators: *Amani Al-Kofide, Nicy Joseph, Rubina Jamil Malik, Walid Aly Mourad, Yasser Khafaja*

Project Description

As per title.

Project Title: A Prospective Study of Invasive Fungal Infections Among Pediatric Patients 0-14 Years of Age With Hematological Malignancies at KFSH&RC and KFNCCC&R.
RAC Project #: 2041006
Principal Investigators: *Ibrahim Bin Huusein*
Co-Investigators: *Asim Belgaumi*

Project Description

As per title.

Project Title: Thrombosis in Childhood Acute Leukemia at KFSH&RC and KFNCCC&R January 2000-December 2002.
RAC Project #: 2031051
Principal Investigators: *Mahasen Saleh and Naima Al-Mulla*
Co-Investigators: *Hassan El-Solh, Ashraf Radwan, Emad Moussa, Ibrahim El-Hassan, Arlene Maculangan*

Project Description

As per title.

Project Title: Retrospective Review of Pediatric Patients Diagnosed With AML and Treated at KFSH&RC Jnuary 1998 - July 2002.
RAC Project #: 2031037
Principal Investigators: *Mohd Al-Mahr and Ashraf Radwan*
Co-Investigators: *Asim Belgaumi, Mouhab Ayas, Mohasen Saleh, Nicy Joseph, Rubina Jamil Malik*

Project Description

As per title.

Project Title: Pharmacokinetics of Metotrexate in Children With Acute Lymphoblastomic Leukemia: Correlation With Outcome.
RAC Project #: 2021004
Principal Investigators: *Abdallah Al-Nasser*
Co-Investigators: *Samir Al-Rawithy, Mohammed Shoukri, Hassan El-Solh, Rana Al-Mulla, Raghad Al-Saad, Tarik Owaidah, Amy Silo, T. Saad*

Project Description

As per title.

Project Title: Translational Initiatives in Lymphoid Malignancies.
RAC Project #: 2020015
Principal Investigators: *Asim Belgaumi, Shahab Uddin Khan*
Co-Investigators: *Hassan El-Solh, Kishore Bhatia, Khalid Abu-Khabar, Brian Meyer, Khawla S. Al-Kuraya, Azhar Hussein, Rong Bu, Abdul Khalid Siraj*

Project Description

As per title.

Project Title: Expression of P. Glycoprotein in Pediatric ALL at KFSH&RC Using Flow Cytometry Analysis.
RAC Project #: 2020004
Principal Investigators: *Abdallah Al-Nasser*
Co-Investigators: *Zuha Al-Mukhlafi, Khalid Al-Hussein, Nasser El-Kum, Fawaz Al-Kasim, Mustafa Khalaf, Hassan El-Solh, Raghad Al-Saad, Amie Silo*

Project Description

As per title.

Project Title: Flow Cytometric Analysis in Childhood Acute Lymphoblastic Leukemia (ALL) in KSA: A Prospective Study of Expression and Correlation With Outcome (MINRESD).
RAC Project #: 2001007
Principal Investigators: *Abdallah Al-Nasser*
Co-Investigators: *Hassan El-Solh, Fawaz Al-Kasim, Mustafa Khalaf, Raghad Al-Saad, Tarik Owaidah, Nasser El-Kum, Khalid Al-Hussein, Amie Silo*

Project Description

As per title.

Project Title: The Outcome of Patients With HLH Treated With Immuno-Chemotherapy Followed by SCT: A Single Centre Experience.
RAC Project #: 2081052
Principal Investigator: *Ali Al-Ahmari*
Co-Investigators: *Mouhab Ayas, Abdlh Al-Jefri, Amal Alseraihy, Ibrahim Al-Fawaz, Mahasen Al-Saleh, Hassan El-Solh*

Project Description

As per title.

Project Title: The Outcome of Children With Constitutional Single Cytopenia Post Allogeneic STS From Matched Related Donor: A Single Centre Experience.
RAC Project #: 2071049
Principal Investigator: *Ali Al-Ahmari*
Co-Investigators: *Ashraf Radwan, Mouhab Ayas, Abdlh Al-Jefri, Amal Alseraihy, Mohammad Al- Mahr, Samira Rifai, Hassan El-Solh*

Project Description

As per title.

Project Title: The Outcome of Children With Post Allogeneic SCT - Comparison Between Two Conditioning Regimens.
RAC Project #: 2061079
Principal Investigator: *Mouhab Ayas*
Co-Investigators: *Abdlh Al-Jefri, Amal Alseraihy, Asim Belgaumi, Ali Al-Ahmari, Mohammad Al-Mahr, Samira Rifai, Ahraf Radwan, Hassan El-Solh*

Project Description

As per title.

Project Title: Allogeneic Stem Cell Transplantation Using Cord Blood as the Source of Stem Cells.
RAC Project #: 2031002
Principal Investigator: *Mouhab Ayas*
Co-Investigators: *Hassan El-Solh, Mohd Al-Mahr, Abdlh Al-Jefri, Samira Rifai, Saadah Mansour, M. Al-Jurf*

Project Description

As per title.

Project Title: The Use of Reduced Intensity Regimen in the Conditioning of Patients With Immune Difficiency Disorders Undergoing Allogeneic Stem Cell Transplantation (SCT).

Principal Investigators: *Mouhab Ayas and Abdul Aziz Al-Ghonaim*

Co-Investigators: *Ali Al-Ahmari, Abdlh Al-Jefri, Amal Al-Seraihy, Hassan El-Solh, Nasser El-Kum, Hamoud Al-Musa, Hassan Al-Dhekri, Saleh Al-Muhsen, Tarik Owaidah*

Project Description

As per title.

Project Title: HSCT in Children With Griscelli Syndrome.

RAC Project #: 2081044

Principal Investigator: *Ali Al-Ahmari, Mouhab Ayas and Al-Mousa*

Co-Investigators: *Al Saud, Amal Al-Seraihy, Saleh Al-Muhsen, Mohd Al-Mahr, Hassan Al-Dhekri, Hassan El-Solh*

Project Description

As per title.

The Department of

SURGERY

Surgery

CHAIRMAN

Mahmoud Ashour, MD

The Department of Surgery is dedicated to the best patient care, teaching and research. At the end of 2009, the department had 8 RAC approved / ongoing and completed 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.

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 ACTIVITIES

Project Title: Study of the Association Between HLA-DRB1 Alleles and Vogt-Koyanagi-Harada Disease in Saudi Patients.
RAC Project #: 2050034
Principal Investigator: *Dr. Khalid Tabbara*
Co-Investigators: *Khaled Al Hussein, Alia Iqniebi, Abdullah Al-Suliman, Ameera Gaafar, Gamal Mohamed*

Project Description

Vogt-Koyanagi-Harada (VKH) disease is an immune-mediated disorder with autoimmune insult directed against antigens associated with melanocytes. Previous studies have shown an increased risk among certain HLA genotypes and it has been suggested that HLA-DRB1 gene is one of the candidate genes for susceptibility to VKH. In Saudi Arabia, there has been no study on genetic predisposition among VKH patients. Therefore, purpose of this study was to investigate the association of HLA-DRB1 alleles with VKH patients in Saudi Arabia. A total of 30 patients with VKH and 29 control subjects were matched by age and sex were included. Genomic DNA was isolated from peripheral blood. The determination of the HLA-DRB1 alleles was carried out by ATRIA GENETICS (AllelSEQR HLA Sequencing Kit). PCR Amplification of the HLA-DRB1 gene was carried out by gene-specific PCR. Results: There was no statistically significant difference in the HLA-DRB alleles 01, 0101, 0102, 0301, 04, 0403, and 0404 between VKH patients and control subjects. Eight (40%) out of 20 patients with VKH had positive HLA-DRB1 *0405 compared to two (26%) out of 19 control subjects. There was a statistically significant difference in the prevalence of HLA-DRB1 *0405 between the VKH patients and control subjects ($p < 0.05$). Other HLA-DRB1 alleles including *0701, 1001, 1101, 1112, 1301, 1302, 1303, 1501 and 1502 showed no statistically significant difference between the two groups. 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.

Progress

Completed on 17 Jan 2009.

Project Title: Saudi Optical Coherence Tomography for Saudi Diabetic Macular Edema Study.
RAC Project #: 2091011
Principal Investigator: *Dr. Selwa Al Hazzaa*
Co-Investigators: *Dr. Faisal Al Qahtani and Dr. Amal Al Hemidan*

Progress

Ongoing.

Project Title: Persistent Hyperinsulinemic Hypoglycemia of Infancy (Nesidioblastosis): Pathological Stratification.
RAC Project #: 2071010
Principal Investigator: *Dr. Saud Al-Shanafey*

Project Description

Looking at the pathology of patients with Nesidioblastosis and check if it has any input on outcome.

Progress

Ongoing.

Project Title: Wilm's Tumor and Breast Feeding.
RAC Project #: 2071004
Principal Investigator: *Dr. Selwa Al Hazzaa*
Co-Investigators: *Fawaz Ibrahim and Salman Taghreed*

Project Description

To check if there is any relation between breast feeding & Wilm's tumor.

Progress

Ongoing.

Project Title: Renal Tumors in Infants.
RAC Project #: 2071009
Principal Investigator: *Dr. Saud Al-Shanafey*
Co-Investigator: *Fawaz Ibrahim*

Project Description

Simple review of renal tumors in infants, descriptive study.

Progress

Ongoing.

Project Title: External Pressure Compression for Umbilical Hernia Management in Infants: Randomized Clinical Trial.
RAC Project #: 2071070
Principal Investigator: *Dr. Saud Al-Shanafey*
Co-Investigators: *Ali Al-Zahrani, Fahad Hazzani, Dowaigh Abdullah, Qidwai Sara*

Project Description

Randomized clinical trial to check if occlusion treatment benefits patients with umblical hernia.

Progress

Ongoing.

Project Title: Surgical Management of Neonatal Severe Hyperparathyroidism: One Center's Experience.
RAC Project #: 2091021
Principal Investigator: *Dr. Saud Al-Shanafey*
Co-Investigator: *Dr. Rana Al-Hossaini*

Project Description

Review of our experience of this disease. This has been concluded and published.

Progress

Completed.

Project Title: Development of Autologous Stem Cell Therapy for Patients with severe Peripheral Arterial Disease of the Lower Limb – A Phase II Non Ramdolized Study.
RAC Project #: 2081021
Principal Investigator: *Dr. Nahar Al Anezi, Dr. Shaker Adra and Dr. AlHumaidan*

Project Description

Critical limb ischemia is a major health problem. Despite available revascularization modalities ie surgical on angioplasty, up to 40% of those patients end up with major amputation and subsequent disabilities.

In this project, we use autology transplant of (MNCS) derived from either bone marrow or peripheral blood to promote the growth of collateral blood vessels and therefore to improve the symptoms and avoid major amputation.

Progress

Completed.

Project Title: Phase II Prospective Study of the Clinical Efficacy of Autologous Stem Cell Transplantation in Patients with Critical Limb Ischemia
RAC Project # 2081-026
Principal Investigator: *Dr. Saad Al Garni*
Co-Investigators: *Dr. Hazaa Al Zahrani and Dr. Said Yousuf*

Project Description

The aim of this project is to investigate the ability of stem cell to generate a new small blood vessel 'collateral' to carry blood from patent proximal artery to distal limb 'leg foot' in order to overcome the ischemia and prevent amputation in patient all way of vascular reconstruction failed.

Progress

Project is still ongoing with good encouraging result in the first few patients we did.

Main Findings

Stem cell did generate small blood vessel.

PUBLICATIONS

Colorectal

- Abubaker J, Bavi P, Al-Haqawi W, Sultana M, Al-Harbi S, Al-Sanea N, Abduljabbar A, Ashari L, Alhomoud S, Al-Dayel F, Uddin S, Al-Kuraya K. Prognostic significance of alterations in KRAS isoforms KRAS-4A/4B and KRAS mutations in colorectal carcinoma. *J Path*. 2009;219:435-45.
- Jehan Z, Bavi P, Sultana M, Hussain A, Alsbeih G, Al-Sanea N, Abduljabbar A, Ashari L, Alhomoud S, Al-Dayel F, Uddin S, Al-Kuraya K. Frequent PIK3CA gene amplification and its clinical significance in Middle Eastern Colorectal Cancer. *J Path*. 2009;219:337-46.
- Uddin S, Bavi P, Hussain AR, Alsbeih G, Al-Sanea N, Abduljabbar A, Ashari LH, Alhomoud S, Al-Dayel F, Ahmed M, Al-Kuraya KS. Leptin Receptor Expression in Middle Eastern Colorectal Cancer and it's Potential Clinical Implication. *Carcinogenesis*. 2009;30:1832-40.
- Uddin S, Hussain AR, Ahmed M, Abubaker J, Al-Sanea N, Abduljabbar A, Ashari L, Alhomoud S, Al-Dayel F, Bavi P, Al-Kuraya K. High prevalence of fatty acid synthase expression in Middle Eastern colorectal cancers and its potential role as a therapeutic target. *Am J Gastroenterol*. 2009;104:1790-801.

Pediatrics

- Saud Al Shanafey, Zakaria Habib, Saleh Al Nassar. Laparoscopic Pancreatectomy for Persistent Hyperinsulinemic Hypoglycemia of Infancy. *Journal of Ped Surg*, 2009; 44: 134-138.
- Al Shanafey S. Laparoscopic versus Open Pancreatectomy for Persistent Hyperinsulinemic Hypoglycemia of Infancy. *J Pediatr Surg* 2009 May; 44(5): 957-61.
- Al Shanafey S, Habib Z, Al Nassar S. Laparoscopic Pancreatectomy for Persistent Hyperinsulinemic Hypoglycemia of Infancy: Preliminary Results. *J Pediatr Surg* 2009 Jan; 44(1): 134-8; Discussion 138.
- Al Shanafey S, Al Zaharani A, Al Ballaa A. Surgical Residents' Satisfaction with Current Surgical Training Program in Riyadh Area. *Ann Saudi Med* 2009 Sep-Oct; 29(5): 388-92

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- Al-Qattan MM, Al-Zahrani K, Al-Omawi M. The bifid median nerve re-visited. *Journal of Hand Surgery*, 34E:212-214, 2009.
- Al-Qattan MM, Al-Tamimi A. Localized hand burns with or without concurrent blast injuries from fireworks. *Burns*, 35:425-429, 2009.

Ophthalmology

- Dr. Khalid Tabbara, Ahmad Al Ghamdi, Fahad Al Mohareb, Mouhab Ayas, Naeem Chaudri, Fahad Al Sharif, Hazzaa Al Zahrani, Said Y. Mohammed, Amr Nassar, Mahmoud Al Jurf. Ocular findings following Allogenic Hematopoietic Stem Cell Transplantation. Submitted for Publication.
- Dr. Faisal Al-Qahtani, Dr. Khalid Tabara, Dr. Keith Wedin, Dr. Selwa Al Hazza, Dr. Saad Al Haddab. Ocular Infection following Solid Organ Transplantation. *Ophthalmology* 2009 Jun; 116(6):12-32.
- Al Hazzaa SAF, Stark W, Bressler N. Progression of Age-Related Macular Degeneration after Cataract Surgery. *Archives of Ophthalmology*, 2009;127(11):1412-1419.
- Safieh A.L, Aldamesh MA, Shamseldin H, Hashem M, Shaheen R, Alkuraya H, Al Hazzaa SAF, Al-Rajhi A, Al-Rajhi A, Alkuraya FS. Clinical and Molecular Characterization of Bardet-Biedl Syndrome in the Saudi Population: The Power Homozygosity Mapping. *J Med Genet doi*; 10.1136/jmg. 2009.070755; 2009.
- Al-Muhsen S, Al-Hemidan AI, Al-Shehri A, Al-Harbi A, Al-Ghonaium A, Al-Saud B, Al-Mousa H, Al-Dhekri H, Arnout R, Al-Mohsen I, Alsmadi O, Ocular Manifestations in Chronic Granulomatous Disease in Saudi Arabia. *J AAPOS* 2009; 13: 396-399.
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- Aldahmesh MA, Al-owain M, Alqahtani F, Al Hazzaa SAF, Alkuraya FS. A Null Mutation in CABP4 Causes Leber's Congenital Amaurosis-like Phenotype. Accepted for publication in *Medical Genetics*.

- Dong LM, Stark WJ, Jeffreys JL, Bressler SB, Solomon SD, Al Hazzaa SAF, Bressler NM. Progression of Retinopathy after Cataract Surgery in patients with Diabetes. Submitted for publication.

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- M. Rafay, H. ElBawab, W. Kurdi, K. Al Kattan, Diaphragmatic Fenestrations in Catamanial Pneuthorax: a Management Strategy, *Asian Cardiovasvcular & Thoracic Annals* 2009 Vol. 17 No. 1, 70 – 72.
- H ElBawab, W. Saleh, K. Al-Kattan, et al, Clinical Use of Combined PET/CT in Recurrence of Thymoma, submitted to *Annals of Thoracic Surgery*, January 2009.
- H. ElBawab, W. Hajjar, K. Al Kattan et al, Plasmapheresis before Thymectomy in Myasthemia Gravis Routine vs Selective Protocols, European *Journal of Cardio-Thoracic Surgery* 35 (2009) 392 – 397.

The Department of

UROLOGY

Urology

The Department of urology aims to create a research community for major urologic diseases and syndromes within the KFSHRC mission interests. It's broad objectives are to: 1) provide an interdisciplinary and multidisciplinary foundation and resource for collaboration among basic, translational, and clinical researchers in the field of urologic disease; and 2) attract investigators with unique scientific expertise and new investigators to study urological diseases and disorders.

CHAIRMAN

Waleed Al Khudair, MD, FRCSC

RESEARCH ACTIVITIES

Project Title: Pilot Study on Penile Auto-Transplantation in the Baboon: Functional Outcome.
RAC Project #: 2080018
Investigators: *Raouf Seyam, MD, Raafat Mohamed El-Sayed, DvM, Falah Hassan Al Mohanna, DvM*

Project Description

Penile tissue loss is not a rare condition. Congenital abdominal wall defects are associated with penile agenesis and urethral anomalies. Complex surgical reconstruction is unsatisfactory cosmetically and functionally. Penile tissue loss may occur due to trauma or genital mutilation. Autotransplantation has been reported in humans with variable degrees of success. Recently composite tissue allotransplantation (CTA) has succeeded for the hand, face and larynx. This has encouraged us to contemplate penile tissue allotransplantation. A prior requisite for such a proposal is to insure that autotransplantation technique is successful and postoperative recovery is uncomplicated. This is important before moving ahead to propose transplantation in the presence of immunosuppression. The penis of the monkey has the closest anatomy and physiology to the human penis. The data acquired during experimental research using the simian penis cannot be duplicated in other large animals like the dog or sheep because of major differences in structure and mechanism of erection. Small animals like the rat are very challenging to work with because of the small penile size. We have used previously the baboon and we have an ongoing project for surgical correction of Peyronie's disease in the baboon penis.

We proposed a pilot study in a limited number of baboons to demonstrate the possibility of autotransplantation of the penis and uncomplicated postoperative recovery of sexual function.

Findings

We have autotransplanted the penis in 2 baboons. Microsurgical anastomosis of the corpora cavernosa and doral neurovascular bundle was successful. The high hyperactivity of the baboon in the post operative period and self mutilation of the implanted penis resulted in infection and autoamputation. The success of further implantations depends on developing methods to protect the implantation sight from self manipulation for several days to permit adequate healing and take of tissues.

Project Title: Penile Auto-Transplantation in the Rat: Impact of Microsurgical Anastomosis of the Dorsal Neurovascular Bundle.
RAC Project #: 2080022
Investigators: *Raouf Seyam, MD, Said A. Kattan, MD, Lina Assad, MD, Rafat El-Sayed, DvM, Falah Hassan Al Mohanna, DvM*

Project Description

Penile allotransplantation might be a viable option for patients needing penile reconstruction. Basic questions need to be answered before contemplating clinical application. It is not known how transplantation and immunosuppression affect erectile tissue, urethra and penile growth. We herein evaluate autotransplantation of the rat penis cut distal to the urethral bulb as a first step towards proceeding for allotransplantation.

Findings

We have presented our results in the annual research meeting showing that cavernous tissue survival is feasible after autotransplantation for up to 3 months. The improvement of the surgical technique is underway to improve survival of the skin and urethra. Anesthesia and post operative recovery conditions are being improved to assure excellent animal survival and recuperation.

Project Title: Microvascular Techniques in Surgery for Infertility and Erectile Dysfunction: Training of the Urology Staff.
RAC Project #: 2082001
Investigators: *Raouf Seyam, MD, Said A. Kattan, MD*

Project Description

Training of urology staff members and residents in microvascular techniques to refine their skills in

surgge4ries on the vas deference, epididymis, testes and penis. These surgeries are carried out in the clinical setting in our department for infertility and erectile dysfunction.

Findings

Residents, assistant consultants and consultants have used the microsurgical facility to hone their skill and acquire new techniques applicable to surgery of male infertility and erectile dysfunction.

Project Title: Rodent Acute Animal Model for Organ Xenotransplantation: Microvascular Surgical Training.
RAC Project #: 2092001
Investigators: *Raouf Seyam, MD, Dr. Waleed Al Khudair, Dr. Ranjit S. Parhar*

Aim

Our main goal is to provide the animal models necessary to push forward research in the fields of xenotransplantation and treatment of myocardial infarction in this institution. Our long term plan is to reproduce in our lab hamster to rat and mouse to rat renal and heart xenotransplantation models as an initial step to proceed for a survival transplantation models. The successful transplantation models will form the surgical platform for experimenting with novel immunosuppression techniques. The purpose of this proposal is to provide in acute non-survival animal experiments the training necessary to achieve successful renal transplantation, myocardial infarction and heart transplantation. To achieve the skills needed to produce these models, extensive training in non-survival experiments is required. Establishing a stable safe anesthesia method is needed where the long duration of the procedure, blood loss, hypothermia and toxicity of drugs may compromise the results. The end point of each acute experiment is to have well perfused kidney and a viable beating heart for 30 minutes before sacrifice.

Findings

Vascular anastomosis with good organ perfusion and complete hemostasis has been attempted in our lab. The results are encouraging but need relentless work to reach that goal. The most demanding part of the surgery is the venous anastomosis to the inferior vena cava. We transplanted the left kidney into the abdominal cavity of the recipient rat using end to side renal vessel to aorta and inferior vena cava anastomosis. The ureteric implantation is challenging because of its delicate blood supply and narrow lumen. Attempts of sutureless implantation and Boari flap anastomosis are underway. We carried out rat to rat cardiac transplantation in several animals and succeeded in having a beating transplanted heart for a few minutes post transplantation in 2 rats. The use of freshly prepared cardioplegic solution to flush the great vessels helped achieve this result.

Project Title: Outcome of the Laparoscopic Versus Open Nephroureterectomy for Upper Tract Urothelial Tumors.
RAC Project #: 2091062
Investigators: *Dr. Khalid Al Othman, Dr. Mahmoud Sherief*

Project Description

Upper tract urothelial carcinoma (UTUC) is not a common disease, accounts for 5–10% of all renal tumors and 5–6% of all urothelial tumors. Nephroureterectomy (NU)has been the standard of care for UTUC. Since 1991, Conventional open NU is being replaced by laparoscopic nephroureterectomy (LNU) as a treatment option for UTUC. It is increasingly being used instead of open nephroureterectomy (ONU) but the evidence of equal oncologic effectiveness is still lacking. We reviewed our experience at KFSHRC regarding perioperative outcome and the oncologic outcomes in both LNU versus ONU.

Patients and Methods

This is a retrospective comparative study for all patients between years (2000 and 2008) with UTUC treated at our institution underwent nephrouretrectomy either open or laparoscopic Thirty seven patients with non-metastatic UTUC were enrolled patient's full charts data were reviewed. 20 patient open (group1) and 17 patient laparoscopic (group2).

Findings

Both groups are matched regarding age, sex and performance status. Operative times were comparable, while mean blood loss and hospital stay were significantly lower in group 2; 882.5 ml versus 523 ml and 9.2days versus5.9 days respectively. In a Median follow-up of 46 mos, local recurrence was comparable but more in ONU. Bladder recurrence was higher in LNU; 12 versus 7 patients. Time to recurrence was shorter in LNU; 15.2 mos versus 20.7mos. Over-all survival is comparable but in favor with LNU, 71%for LNU versus 63%for ONU. The limitations of our study include the small sample size and the personal choice of laparoscopic technique.

Conclusion

Although perioperative outcomes are in favor of LNU, it has a higher bladder recurrence rate. Larger number of patients in a randomized controlled study would be appreciated.

Project Title: The Correlates of the Male Sexual Dysfunction in Liver Transplantation Patients and the Impact of Management.
RAC Project #: 2091016
Investigators: *Dr. Said Kattan, Dr. Raouf Seyam, Dr. Hatem Khalaf, Dr. Mohamed Alsebayel, Dr. Ahmad El-Sakka*

Project Description

During the past 20 years, orthotopic liver transplantation has emerged as the treatment of choice for end stage liver diseases of various causes. Most transplant centers reported 1-year survival rates for adult transplant recipients of about 80-90% and 9-year survival rates of 55% (Seaberg, 1997). As the clinical outcomes of orthotopic liver transplantation continue to improve, resulting in fewer postoperative complications and better immunosuppression, other outcomes, such as health-related quality of life, become important targets of evaluation.

The purpose of the research is to evaluate the prevalence of sexual dysfunction among patients waiting of have received liver transplantation. The underlying causes will be investigated and proper treatment will be offered.

Patients awaiting liver transplantation and those who have received it will be subjected to a questionnaire by an interviewer. No additional investigations will be added to the routine care of liver transplantation patients as deemed necessary by the transplantation team. Those patients who demonstrate sexual dysfunction will be referred to the urology clinic where routine clinical examination and investigations will be carried out to diagnose and treat their problem as routine care for these cases. Follow up in transplantation clinic and urology clinic will continue every 3 months at least for 2 years as routine follow up of these patients is necessary for routine management. Additionally, the questionnaires will be applied to patients followed up for the purpose of this research project every 3 months during their clinic visits.

Project Status

The proposal is under evaluation by the ORA and rebuttal to suggestions were going on to the end of 2009.

Project Title: Long Term Outcome of Renal Cell Carcinoma (RCC) Patients Treated With Radical or Partial Nephrectomy in the last 12 years.
RAC Project #: 20910632
Investigators: *Dr. Waleed Al Khudair, Dr. Mahmoud Sherief, Dr. Mohammed Al Otaibi*

Project Description

Renal cell carcinoma (RCC) represents almost 85% of newly diagnosed malignancies of the kidney. There is an increase in the rate of renal cell carcinoma of 2.3% to 4.3% yearly. This increase may partially be attributable to early detection through the widespread use of noninvasive imaging techniques. This has also been recognized in our eastern populations.

Radical Nephrectomy (RN) has been the gold standard treatment for RCC in the last 2 decades. However, the risk of renal function deterioration after RN has now been well documented. Consequently there has been a

constant development of Nephron Sparing surgery (NSS) to avoid unnecessary nephron waste. Disease specific survival rates are similar for RN and NSS in such cases Regardless of tumor size. Many reports have argued the effect of surgical approach, surgical margin and adrenal involvement and if affecting the oncological outcomes. Aim: To establish standards for future comparisons we must fully appreciate the efficacy, safety and limitations of both radical and NSS for RCC. Therefore, we will review our experience and report results for the last 12 years at KFSHRC and also to determine the cancer control regarding to all these variables.

Patient Population

All patients between 1995 and 2008 with suspected RCC treated at our institution. We will collect certain data, including age at surgery, gender, symptomatic disease at presentation, surgical technique, operative time, blood loss, preoperative and postoperative serum creatinine in mg/dl and complications. Fuhrman grade, 2002 TNM stage, tumor size and pathological data on the surgical specimen, ie margin status, disease progression and outcome

Findings

Data collection

We reviewed our medical records for the available charts and started to review patients that fulfill our inclusion criteria in an excel sheet. Then we will review all the selected charts for having our final population of the study.

Data will be collected from charts and will be arranged in tables and sheets on which we will our statistical analysis. Editing and interpretation of results will follow.

Project Title: Infection Risk with Noble-Metal Alloy Latex Urethral Catheters in Intensive Care Unit Patients.
RAC Project #: 2091097
Investigators: *Dr. Waleed Al Khudair, Dr. Alaa Mokhtar Hammad, Dr. Nabil Abouchaleh, Dr. Abdelmuniem M. Eldali*

Project Description

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

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

Project Status

This research project is currently being reviewed by the Office of Research Affairs.

Project Title: Establishment of the Prevalence Rate of Bladder in The Kingdom of Saudi Arabia.
RAC Project #: 2091094
Investigators: *Dr. Waleed Al Khudair, Dr. Mohammed Al Otaibi, Dr. Hassan Al Zahrani, Dr. Raouf Seyam, Dr. Mohamed Shoukri*

Purpose of the Research

We set out to early detect bladder cancer in populations at high risk in Saudi Arabia, namely, men above 50 years o ld and heavy smokers living in all regions of the Kingdom. We will screen men at high risk for bladder cancer from representative regions of the Kingdom. Men above 50 years old or heavy smokers are eligible for screening. Urine dipstick test for hematuria and NMP22 urinary tumor marker test will be carried out. Patients with hematuria and or positive urine tumor marker are further evaluated clinically and by laboratory tests, CT and cystoscopy. Patients with cancer bladder will be referred to KFSH&RC for further management.

Results

The prevalence of cancer bladder in high risk population in Saudi Arabia will be determined and patients are offered early treatment.

Project Status

This research project was submitted to ORA and KACST for review.

Project Title: Transitional Cell Carcinoma of the Bladder in a Young Age Group.
RAC Project #: 2091085
Investigators: *Dr. Khalid Al Othman, Dr. Naif Al Hathal*

Introduction

Transitional cell carcinoma (urothelial) is the most common type of bladder tumors. The peak incidence in the 7th decade. It is among the ten most prevalent tumors in Saudi Arabia. Most of urethelial bladder tumors are superficial and up to 25% of them will progress into muscle invasive disease requiring radical surgery and 10% are metastatic at presentation. Due to the high prevalence of this disease in elderly, extensive data is available on the surveillance, treatment and follow up protocols in this age group. Bladder urothelial tumors, however, occur rarely in the first 2 decades of life and commonly of mesodermal origin. Until 1996, only 100 reported cases among which the largest series has described these tumors as low grade and rarely recurrent. On the other hand, some other reports have described recurrence and death due to metastatic disease in the same age group. The rarity of urothelial tumors in this age group and the variety of presentation and prognosis has made conclusions regarding the etiology, invasiveness, treatment and surveillance difficult to formulate. In literature review, only few scattered case reports exist and one of the largest series on transitional cell carcinoma in 20 year old ad less population was reported by Samson et al on 2005 with total number of 23 cases. He described a male predominance and the most common presentation was painless gross hematuria, all tumors were solitary and without invasion. Only 3(13%) had recurrence and all had a favorable outcome. Lazema et al, however, reported aggressive, high grade transitional cell carcinoma in 3 year old boy despite radical cystectomy, chemotherapy and radiation. This has motivated us to conduct a retrospective study to report all patients and transitional cell carcinoma who are 20 year old or less to further support the literature with more data in this rare disease.

Objective

To identify the probable risk factors, stratify the natural history and outcome of bladder transitional cell carcinoma in pediatric age group and younger adults.

Material and Methods

A retrospective chart review of all patients 20 year old and less who were diagnosed to have bladder transitional carcinoma at King Faisal Specialist Hospital and Research Centre from 1975-2006. Genetics are out of focus of this study.

Demographic, clinical and pathological data will be emphasized in tables and forms. Transurethral resection of bladder tumor (TURBT), any given adjuvant therapy, initial pathological stage and follow up disease recurrence of progression will be recorded.

Project Title: Congenital Adrenal Hyperplasia: A Retrospective Study of Long Term Outcome.
RAC Project #: 2091022
Investigators: *Dr. Waleed Al Khudair, Dr. Raouf Seyam Dr. Mohammad Al Abdulaaly, Dr. Nadia Sakati, Dr. Nabil K. Bissada*

Project Description

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is one of the most common known autosomal recessive disorders. Because CAH has a high frequency, a variable presentation in children and adults, and potential complications, a thorough understanding of the disorder is of great importance to clinicians. Since the discovery of cortisone therapy and the addition of mineralocorticoid supplementation, the morbidity and mortality of patients with classic disease have markedly decreased, and

these patients now have a long life span. Thus, long-term consequences of current treatments are an important consideration. There are many unresolved clinical problems in the management of classic 21-hydroxylase deficiency in both males and females. Among the most critical are inadequate response to glucocorticoid and mineralocorticoid replacement therapy, iatrogenic Cushing syndrome, adult short stature, and oligo-amenorrhea and infertility in women. Females born with genital ambiguity may need surgical repair in the first few months of life, during childhood and early adulthood. Adrenal rest tumors are most commonly found I the testes of men with congenital adrenal hyperplasia and often result in oligo-azoospermia and infertility. The long term psychological impact of CAH, results of cosmetic genital repair and fertility status are needed as many of these patients continue to grow into adulthood. Lessons learned from management outcome may be useful to guide novel diagnostic and treatment strategies for CAH.

Findings

The chart review process is complete. An amendment of phone follow up was approved by ORA and is underway. Analysis of the obtained data shed light on an important aspect of the study which is concerned with the sexual function of adult women with CAH. The following abstract summarized this aspect of the study.

Objective

Classical congenital adrenal hyperplasia (CAH) presents in early childhood with salt loosing crisis and ambiguous genitalia. Earlier detection and improvements in medical and surgical genital reconstruction have resulted in an increasing number of patients reaching womanhood. There is a paucity of data on the long term outcome in women born with congenital adrenal hyperplasia.

We set out to review the progress and sexuality of adult women treated in our hospital for CAH.

Material and Method

We reviewed the medical records of women 20 years or older with the diagnosis of CAH. We identified the clinical history, laboratory data, medical management, surgical reconstruction, marital status, evidence of virilization, fertility and condition at last follow-up.

Results

We identified 45 women with mean age 24.3 years (SE 0.6) with the diagnosis of CAH. Mean follow up was 23.2 years (SE 0.7). Patients presented in infancy and childhood with salt loosing crisis mainly, ambiguous genitalia only or both. Few patients presented late with severe virilization. Prader gential grade was III-IV or higher in 37 patients. One stage clitroplasty, valvoplasty and vaginoplasty were performed in 21 (47%) girls at the age of 2.5 yrs (SE 0.4). A deferred vaginoplasty was carried out in 11 (24%) patients at the age of 6.1 years (SE 1.1). Revision surgery was carried out in 13 (29%) patients. Menarche occurred at 14.1 years (SE 0.6). Women had an average weight of 63.7 kg (SE 3.8) and height of 146.7 cm (SE 2.6). Cosmetic genital appearance was good to excellent in 28 (62%) patients. Severe vaginal stenosis was found in 6 (13%) patients. Ten women had virilization in the form of harsh voice and or hirsutism. Three patients are treated for depression with one attempted suicide. Only 5 women were married at mean age of 18.5 yrs (0.9 SE) for a period of 5.8 yrs (SE 1.3). One woman had vaginal trauma and needed surgical repair, another has dysparunia often and 3 remain with no dysparunia. Four ladies conceived, 3 unassisted and 3 delivered one normal child. One patient was divorce within 1yr.

Conclusion

CAH has a significant impact on the sexuality of women in their adult life. Most patients in early adulthood remain single with variable virilization effects. Few women are able to lead normal sexual life and give birth to normal children.

Project Title: CNeurogenic Bladder in the Saudi Population: Prevalence, Morbidity and Botox Treatment Outcome (KACST).
RAC Project #: 2091004
Investigators: *Dr. Waleed Al Taweel, Dr. Raouf Seyam Dr. Alaa Mokhtar, Dr. Khaled Fouda*

Abstract

Neurogenic Bladder is a common and significant complication of neurologic disease. It is an important and frequent cause of recurrent urinary tract infection and renal failure in those patients. The rise of intravesical pressure is underlies the development of renal failure. Periodic and vigilant urodynamic testing and urine analysis and culture prevent the occurrence of these complications. Several patients do not respond to oral medications that inhibit bladder overactivity. Those patients previously were candidate for major surgery to reduce bladder pressure. Recent studies showed that botox intravesical injection using endoscopy is associated with high success rate in reducing bladder pressure and aliviating recurrent urinary tract infection. The aim of this project is to evaluate the prevalence of neurogenic bladder in major cities large hospitals in the Kingdom of Saudi Arabia. Those patients will undergo periodic renal ultrasound, urine analysis and culture, renal profile and urodynamics. Patients who will not respond to oral medications will be treated by botox intravesical injection. The research team will follow these patients regularly for 3 years.

Background

Patients with spinal cord injury (SCI) usually have permanent and often devastating neurologic deficits and disability. Voiding disorders secondary to neurogenic bladder are usually a result of neurologic conditions, such as spinal cord injury (SCI) or disease, cerebrovascular accident (CVA), traumatic brain injury (TBI), multiple sclerosis (MS), or dementia. Incontinence and urinary retention can cause social embarrassment and added morbidity, such as infections, stones, or renal injury.

Project Status

This research project is under review of the ORA and KACST.

Project Title: A Novel Retractor for Laparoscopic Urologic Procedures: An Acute Study in Dogs.
RAC Project #: 2090020
Investigators: *Dr. Waleed Al Khudair, Dr. Raouf Seyam, Dr. Fayez Almodhen*

Project Description

Laparoscopic surgery applications are expanding to replace open surgical procedure with high safety and efficacy. The advancement of laparoscopic surgery was possible by innovations proved to facilitate surgery, reduce time and permit good visualization and handling of tissues. Retraction and counter traction are major assets in achieving sound surgery. Several retractors have been devised to assist in laparoscopic surgery. These retractors, however, need additional ports which they occupy during surgery. A novel patient approved retractor is described here which is placed intra-abdominally and removed at the end of surgery freeing up all ports for other instruments. We intend to demonstrate the efficacy and safety of this retractor in laparoscopic procedure in acute experiments in dogs.

Materials and methods

Male mongrel dogs weighing 8 to 12 kg under general anesthesia are used. Using standard laparoscopic equipment, the abdomen is insufflated. Three laparoscopic trocars are inserted and used for instrument application and retractor placement. The abdomen is examined and the retractor is inserted and fixed to the inner side of the anterior abdominal wall. Retractor extensions are applied to the desired tissue and tension is applied to expose the site of interest. Standard surgical urologic procedures are carried out in succession using the retractor as an aid. These procedures include pyeloplasty, nephrectomy, cystectomy and prostatectomy. The animal is sacrificed at the end of the experiment with standard euthanasia methods as described later.

Anticipate results

We anticipate that in this setting, we will be able to demonstrate the efficacy and safety of this novel laparoscopic retractor.

Conclusion

Laparoscopic surgery is progressing rapidly to replace many standard open surgical procedures. The innovation

of better instruments facilitates the advent of this minimally invasive surgery. We demonstrate in this experiment the efficacy and safety of a novel patent approved laparoscopic retractor.

Project Status

The project has been approved. The novel retractor is in the manufacture process. Surgery will start once we receive the final product.

Project Title: Genomic and Proteomic Signatures of Prostate Cancer in Middle Eastern and North African (MENA) Populations.

RAC Project #: 2091099

Investigators: *Dr. Lotfi Chouchane, Dr. Khaled Al Rumaihi, Dr. Sami Al Said, Dr. Issam Al Bozom, Joel Malek, Dr. Sheng Zhang, Dr. Sami Khatib, Dr. Mohammed Al Otaibi, Dr. Karim Chahed, Prof. Andre Megarbane, Dr. Raouf Seyam*

Specific Aims

The knowledge of human genetic variation that will come from the human genome sequence makes feasible genomic and proteomic approaches to disease prevention and prediction, in which it will be possible to identify individuals as susceptible by their genome/proteome profile and to prevent disease by targeting interventions to those at risk. Personalized medicine is leading to the need for understanding genetic polymorphism and for promoting racial and ethnic diversity in clinical trials.

Prostate cancer is the most common malignancy in many industrialized countries and the second cause of cancer-related death in Europe and the United States. The incidence of the disease has been increasing in Middle Eastern and North African (MENA) populations. Large databases focused on genetic susceptibility to prostate cancer have been accumulated from population studies of different ancestries, including Europeans and Africans-Americans. MENA populations, however, have been only rarely studied. The aggressive forms of prostate cancer are found frequently in MENA populations.

Hypothesis

Ethnic specific variants on genes involved in different prostate cancer biology pathways along with risk-modifying factors, such as consanguinity, may explain the prostate cancer incidence variability and its clinical heterogeneity across racial/ethnic groups.

Though cancer-oriented genomic and proteomic approaches, the present proposal aims to generate a prioritized panel of genes and proteins involved in prostate cancer risk and progression in MENA populations. More specifically, we will seek the following aims:

Aim 1: Set-up a clinical-pathological database and biological repository (tissue, DNA, serum, urine) of a large population of 700 patients with prostate cancer and 700 age-matched healthy control subjects from 5 MENA countries: Qatar, Tunisia, Jordan, Lebanon and Saudi Arabia.

Aim 2: Through the genome-wide association study (GWAS), we will examine the effect of inherited Single Nucleotide Polymorphism (SNPs) and Copy Number Variation (CNVs) in the risk of developing prostate cancer, disease progression and mortality. We will compare the allele/genotype and haplotype frequencies of more than 900,000 SNPs and more than 946,000 non-polymorphic probes (for detection of the CNVs) in 700 MENA patients with prostate cancer (200-250 cases/year) and the corresponding 700 age-matched control subjects. SNPs and CNVs profiles will be generated and classified according to the tumor aggressiveness defined by Gleason score and DNA policy.

Aim 3: Through a high-throughput proteomic analysis, we will investigate new biomarkers of prostate cancer for better disease diagnosis, stratification and prognosis of the disease. Malignant and non-malignant tissues, serum and urine from patients and controls will be used for protein profiling. This will be complemented by a serological proteomics-based approach (SERPA) to identify tumor antigens that induce a humoral immune response. Investigating, in a large cohort of MENA patients with prostate cancer, the correlation between

the presence of the prostate cancer biomarker candidates in the serum and disease aggressiveness will assess their prognostic values.

The recent establishment of world-class Genomic Core Facility at Weill Cornell Medical College in Qatar along with the well-established Proteomic Core Facility of Cornell University in New York will facilitate the achievement of the aims of the present proposal.

Project Status

The project has been reviewed by the ORA. Rebuttals were made to suggestions by concerned committees.

Project Title: Identification of Novel Diagnostic and Prognostic Markers for Bladder Cancer Through Whole Genome Methylation Profiling (KACST).
KACST Code Number: 09-BI0812-44
Investigators: *Dr. Waleed Al Khudair, Dr. Mohammed Al Otaibi, Dr. Hassan Al Zahrani, Dr. Ahmed Yaqinuddin*

Project Description

Urinary bladder cancer is the 2nd most common urologic cancer worldwide. In Saudi Arabia, the incidence of bladder cancer is rising and is now more frequent than prostate cancer. At present, the diagnosis and monitoring of bladder cancer is largely dependent on cystoscopy and subsequent histological examination of the bladder tissue which is an invasive and expensive procedure. Therefore, there is immense need to develop blood or urine based diagnostic and prognostic markers which can sensitively and specifically detect bladder cancer and can aid in monitoring progression of disease. In this regard, changes in the DNA methylation pattern of genome which are the hallmark of carcinogenesis can be employed to detect free floating tumor DNA in the blood or urine samples of bladder cancer patients. In this study, we will investigate genome wide methylation status of CpG islands in the DNA derived from bladder cancer tissues and their respective controls by employing a promoter CpG gene chip array. This will allow us to identify CpG islands which are distinctively methylated in bladder cancer. These CpG islands or methylation markers will subsequently be tested for their ability to detect tumor DNA derived from bladder cancer tissue using blood samples of cancer and control patients. This study will not only help us develop insight into the epigenetic mechanisms involved in bladder cancer, but will also allow us to develop novel diagnostic and prognostic markers to manage bladder cancer effectively.

Project Status

This project is highly recommended and a process to release the funds is being established.

Project Title: Detection of Incidental Prostatic Adenocarcinoma in Radical Cystoprostatectomy Specimens
Investigators: *Dr. Mohammed Al Otaibi, Dr. Alaa Moukhtar, Dr. Asma Tulba, Dr. Hatem Khoja, Dr. Waleed Al Khudair*

Project Description

It has been hypothized that the incidence of prostate cancer in the Middle East is lower than the Western countries. We aim at detection of incidental adenocarcinoma of the prostate in patients undergoing radical cystoprostatectomy for bladder cancer in King Faisal Hospital and Research Center. After performing radical cystoprostatectomy for carcinoma of the bladder, the prostate specimens will be sectioned at thin intervals and histopathologically evaluated for the presence of carcinoma of the prostate. The results will be analyzed and compared with the published data.

Project Status

This project is currently being reviewed by the Office of Research Affairs.