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

2010
RESEARCH REPORT

THE

RESEARCH CENTRE

RESEARCH REPORT

THE DEPARTMENT OF

Biological and Medical Research

The Department of Biological and Medical Research

Acting Chairman

Futwan Al-Mohanna, PhD, FIBiol, FRSC

Administrative Support Staff

Rita Sison
Robyn Seamer
Moneth Ebora
Hanan Al Shaarawi (Grant)
Cheryl Mijares (Grant)

The Biological and Medical Research Department is one of the oldest departments in the Research Centre whose main function is to support original research that should make a significant contribution to knowledge in medical and biological sciences including but not limited to allergy and aerobiology, breast cancer, cell biology (diabetes and cardiovascular diseases), DNA repair and apoptosis, environmental health, molecular virology and infectious diseases, and the TB Research.

During the year 2010, the department was able to publish 26 full length papers, 3 abstracts, 24 research projects, and 6 projects submitted. 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

- The Atr protein kinase controls UV-dependent up-regulation of p16INK4A through inhibition of Skp2-related polyubiquitination/degradation.
- Shown that stromal fibroblast p16 has cell non-autonomous tumor suppressor function in breast cancer.
- Identification of Non-CpG and CpG cytosine methylation in the BRCA1 promoter in peripheral blood cells from breast cancer-free females.
- Discovery of a novel anti-breast cancer molecule (PAC), with higher efficiency on ER-negative cells.
- The power of gene expression profiling is the ability to understand biology beyond what may be apparent from the study of clinical variables or individual gene markers.
- We identified genes and pathways specifically activated or inactivated during the course of breast cancer progression arising in young women.
- Our genomewide expression and network analysis indicated the dysregulation of DUSP6, PI3K and MAPK pathways; hence targeting these genes/pathways may have potential impact on the treatment of young Saudi breast cancer patients.
- 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.
- DNA fingerprinting for tracing nosocomial pathogens in our hospital and other hospitals inside and outside Riyadh.

Allergy and Medical Aerobiology

Head

Syed M. Hasnain, PhD, FACAAI, FAAAAI

Members

Abdulrahman Al-Suwaine, PhD
Halima Al-Sini
Samia Khan
Alanoud Al-Qassim
Abdulrahman Al-Sobhi
Mubarak Al-Enizi
Cheryl Mijares

The Allergy and Medical Aerobiology laboratory is currently involved in the following Projects (either in progress or awaiting approval/being revised):

1. **Project Title:** Isolation, Purification and Immunochemical Characterization of Allergenic Protein(s) from *Amaranthus viridis* Pollen Grains (RAC Project # 2050 029) – In Progress.
   Investigators: Syed M. Hasnain, Abdulkareem A. Alaiya, Halima Al-Sini, Alanoud Al-Qassim, Mai Al-Mohanna, Mohammed O. Gad-El-Rab.
   Consultant: Prof. Abdulrahman Al-Frayh, King Khalid University, Hospital Clinic
2. Development of Allergotek Diagnostic and Therapeutic Program. (in Progress).
3. Dahran Project (Phase II-Aeroallergens monitoring for a special request) - (in Progress).
4. Characteristics and composition of the falling dust and particulate matter and its health hazards in Riyadh City, Saudi Arabia. King Saud University Collaborative Project (awaiting approval).
5. House Dust Mites and asthma in different cities of Saudi Arabia (proposal submitted).
6. A study of outdoor airborne allergens in relation to asthma and allergies in the Eastern province of Saudi Arabia. King Abdullah International Medical Research Center, King Saud Bin Abdulaziz University for Health Sciences, National Guard Health Affairs (being revised).
7. Holy sites Project: An Investigation of Allergy, Asthma and Outdoor Aeroallergens in the Holy Sites of Saudi Arabia (Submitted to KACST). Principal Investigator (being revised).
8. Development of Allergen Monitoring Services Program (awaiting space).
9. Study on cross-reactivities of allergens using human sera (negotiated with Inmunotek).

RESEARCH PROGRESS

Project description

This project has been approved by the Research Advisory Council (RAC 2050 029), supported by KACST (Grant) ARP-27-11 and has been extended for another year until 2011.

Amaranthus viridis is the most dominant pollen grains in Saudi Arabia, like the ragweed in the United States and therefore needs special attention in this region.

During the year 2010 we concentrated on the following:

1. Biochemical Studies including collection, separation and purification of various Amaranthus species
2. Biochemical studies including extraction of pollen and SDS-PAGE
3. Clinical studies using Skin Prick Test (SPT) in selected and consented patients.
4. Immunochemical studies using sera from positive patients and control subject with their signed consent.
5. Proteomics studies include Immunochemical blotting - identification of protein using patients sera

Pollen Antigens

Pollen samples were defatted with n-butanol and dried. Antigens were extracted in phosphate buffer saline PBS (1:10 w/v) by continuous stirring at 4°C for 72 hrs. the extracts were centrifuged at 10,000 rpm for 30 min, and the supernatant was dialyzed against 85% PBS and lyophilized in small aliquots, kept at –20°C and reconstituted when and as required.

Reconstituted lyophilized powder was sterilized using bacterial filtration and sterilization by passing through 0.45 mm and 0.22 mm filter using Millipore filter units (Millipore, Bedford, Mass., USA) the filtrate saved in sterile vials. 50% Glycerinated Allergenic Extracts were prepared.

Purity and sterility for Extracts were tested by using Brain Heart Infusion agar and Blood agar for 15 days at 37°C, the sterility test was negative.

Protein Estimation

Protein content of each extract was determined by Bradford method.

Sodium dodecyl sulphate polyacrylamide electrophoresis (SDS-PAGE).

The procedure outlined by Laemmli was followed.

SDS-PAGE was carried out using polyacrylamide gel 12% 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.

Skin Test

Skin prick tests were performed on 97 patients, but sera was obtained only from seven patients because of consent was not given by others. (Please, see the clinical part for detail).

Serum samples

Venous blood was drawn from skin test positive patients and sera were separated by centrifugation and stored at -70°C in small aliquots for further use.

Immunoblot

Preliminary studies have been made using Western blot techniques.

For immunoblotting 20µg of total protein of each sample was separated by SDS-PAGE in 12% gel as described above.

Using Tris glycine buffer (0.02M tris, 0.2M glycine, 20% methanol, pH8.3), proteins were then transferred onto polyvinyidene difluoride PVDF membranes at 32V for overnight using Mini-Trans Blotelectrophoretic device (Bio-Rad).

After blotting, unreacted sites on the membrane were blocked by incubating with 5% zero fat milk in 0.05% TPBS.

Highly positive sera from patients were used for immunodetection. The resulting membranes were probed for overnight at 4°C, in all incubations the serum was diluted in the ratio of 1:500 using PBS containing 0.05% Tween20.

Membranes were washed 4 times with washing buffer PBST. Then incubated with antihuman IgE peroxidase conjugate (Sigma, USA) in the ratio of 1:10000 in PBST for one hour.

The lane probed with human serum samples were subjected to autoradiography at room temperature for minutes.

RESULTS

SDS-PAGE was performed on the pollen extracts using 12% acrylamide gels; thereafter the separated proteins were transferred electrophoretically to polyvinylidene difloride (PVDF) membrane and probed with sera obtained from patients that showed positive antibody sensitivity towards Amaranthus species protein extracts.

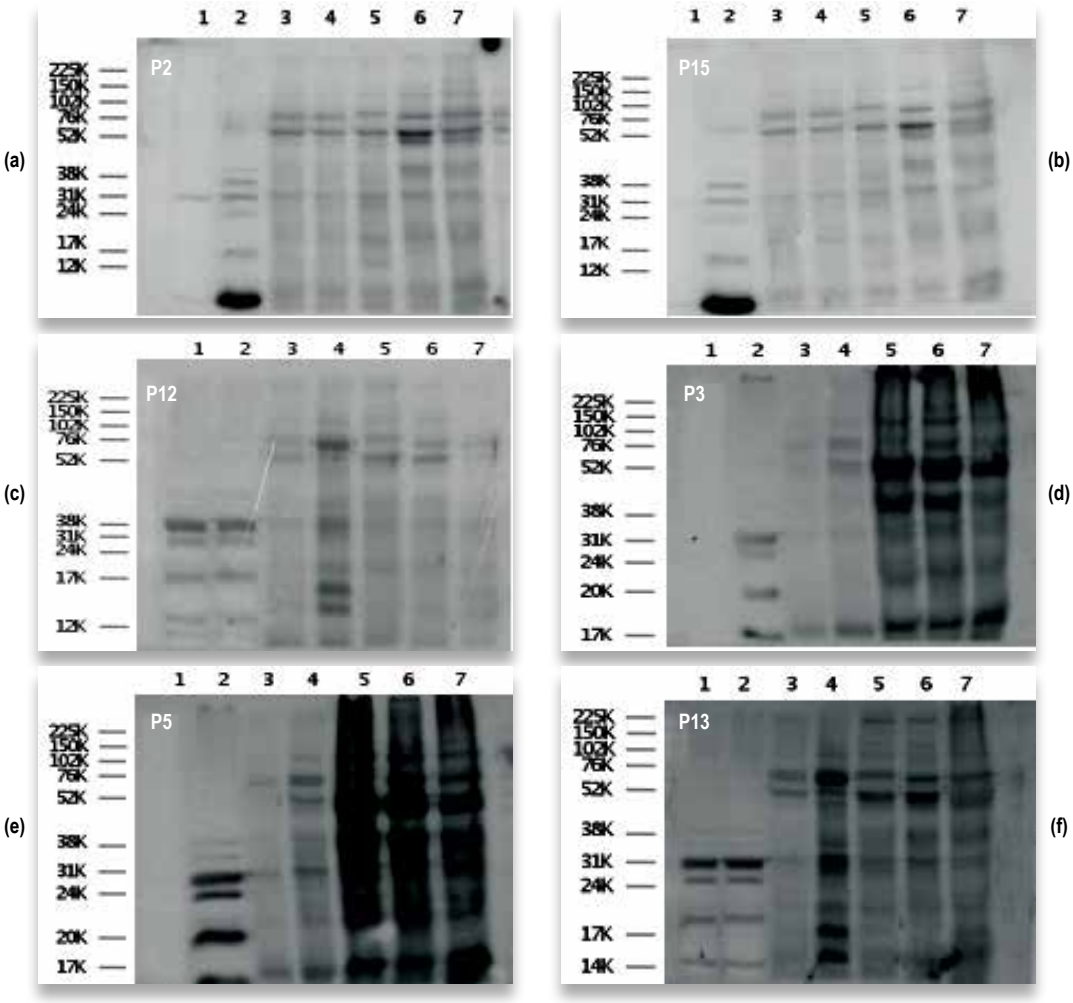
On immunobloting of samples (12 subjects) we found that

83.3% of the Amaranthus sensitized individuals have IgE-binding antibodies to *Amaranthus viridis* (Indigenous) pollen extract.

The 12 patients provided Sera in our immunoblot result confirms that more than 83% of the individuals sensitized with Amaranthus pollen, have IgE binding antibodies to indigenous *A. viridis* pollen.

The major amaranthus allergen defined as binding IgE from most subjects is 76Kda, other IgE-bindingallergens were found at 31, 52, 42, and 17Kda.

Figure 1 (a,b,c,d,e,f): Immunoblot showing Amaranthus species specific IgE binding fractions of antigenic extracts probed with sera of SPT positive patients (p2), (p15), (p12), (p3), (p5), (p13).



1-Amaranthus viridis (Indigenous), 2-A. lividus. (Indigenous), 3-A. retroflexus. (Allergon), 4-A. retroflexus (Greer), 5-A. tuberculatus (Greer), 6-A. hybridus (Greer), 7-A. palmeri (Greer).

In all these figures patients showed allergenicity towards *Amaranthus retroflexus* (L4) a species which is not locally found in Saudi Arabia.

ALLERGY SKIN TEST RESULT

Patient referred to the allergy clinic at King Khalid University hospital with various allergic disorders are skin tested as part of the allergy work-up.

Those suffering from upper and lower respiratory allergy are skin tested by a panel of common prevalent allergens including Amaranthus extract (commercial). Among these patients, those who agree to participate in the study are fully informed about the aim of the study and that the purpose of the research is to investigate the role of *Amaranthus viridis* pollen in patients with asthma and rhinitis in the kingdom of Saudi Arabia. Patients who agreed to participate signed a consent form as approved by the Research Advisory Council (RAC) of KFSH&RC. These patients were tested with Amaranthus extracts prepared at the research center. The vials were supplied to the Allergy clinic with encoded numbers from 1-7. Positive and negative controls were included.

For the purpose of comparisons and statistical analysis the patients were divided into 2 groups as follows.

Group 1: Patients with respiratory allergy who did not agree to participate but were tested by the commercial Amaranthus extract as part of the routine allergy work-up (Total no: 97).

Group 2: Patients with respiratory allergy who agree to participate in the study were tested by the locally- prepared Amaranthus extract. (Total no: 77).

In the first group, out of 97 patients, 26 were positive (26.8%). In the second group, who were tested by the locally-prepared extract, out of 77 patients, 24 reacted positively (31.2%). This reflects that more patients reacted to the locally prepared extract as compared to the commercial extract. This comparison seemed to be important in order to determine the prevalence of sensitivity to Amaranthus pollens in the community.

BIOCHEMICAL STUDIES

Proteomics Analysis of Serum Samples of Patients Exposed to Different Amaranthus Allergens were conducted

This study demonstrate that serum protein profiles induced by Amaranthus allergens are feasible and can aid in discovery of specie specific proteins that can be used in development of Amaranthus specie specific vaccines.

Electrophoresis, scanning and image analysis

Crude serum samples were diluted to a total volume of 350 µl, in a solution containing 8 M urea, 2M thio urea, 0.2% Pharmalyte, 0.3% DTT, 2 M CHAPS and a trace of bromphenol blue. A total amount of 75 µg of protein was loaded on each strip via rehydration using linear pH 4-7 Ready IPG, strips (Bio-Rad, Hercules, and Ca, USA). First-dimension isoelectric focusing was carried out for a total of 45,500 Vh in a PROTEAN IEF cell (Bio-Rad).

Following Isoelectric focusing, the strips were first equilibrated in a 15 ml solution containing (8 M urea, 75 mM Tris (pH 8.8), 30% (w/v) glycerol, 2% (w/v) SDS, and 0.002% bromophenol blue) and reduced with 65 mM DTT for 15 min, followed by 15 min second equilibration in a solution containing 135 mM iodoacetamide. The IPG-strips were then loaded and run on a 12.5% SDS-PAGE criterion mini gel and run over 2 hours at 200V constant until the bromophenol blue dye front had reached the bottom of the gel. The gels were stained with silver nitrate and scanned using a calibrated densitometer, GS 800 and data was analyzed using Progenesis SameSpots software (Nonlinear Dynamics).

RESULTS

Protein expression patterns between different species of Amaranthus samples

Serum samples obtained from seven patients inoculated with different types of Amaranthus as well as sample from 5 healthy subjects as negative control samples 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 548 spots were resolved and more than 95% of the resolved protein spots were successfully matched between all the gels. Representative 2D gel images from one control and one patient serum samples are shown in Figure 2.

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). Sera were collected from patients diagnosed with allergic rhinitis or asthma. Samples were divided into two groups as patients and controls.

Based on their percutaneous skin 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 19 proteins were observed between patient and control samples. These differential changes were considered significant ($P < 0.05$ with 98% CI) using combined ANOVA and more than 2-fold difference in the levels of expression of these protein spots. Two representative 2D gel images from patient and Control serum samples are shown in figure 2 with gel segments indicating two differentially expressed spots between patient and control samples.

These 19 dataset of protein spots were used in the Principal Component Analysis (PCA) and unsupervised hierarchical cluster analysis and the samples were correctly classified into two distinct groups (Figures 3A & 3B). The location and distribution pattern of some of these proteins are shown in Figure 4. Fifteen (15) of the 19 protein spots were at least more than 2-fold highly expressed in the patient group than in control sample The differential expressions of two of these proteins are shown as gel segments in Figure 2.

Figure 2: Representative 2 D gel images from patient (A) and Control (B) serum samples. Gel segments showing two differentially expressed spots between patient and control samples, Crude serum sample was subjected to 2-DE using IPG strip pH 4-7 in the first dimension and 12.5% mini criterion pre cast SDS polyacrylamide gel in the 2nd dimension.

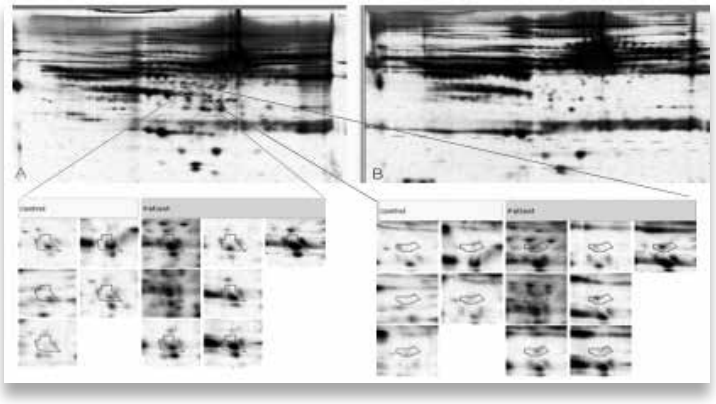


Figure 3A: Principal Component Analysis (PCA) plot using the expression patterns of 19 protein datasets that are differentially expressed between the control and patient samples.

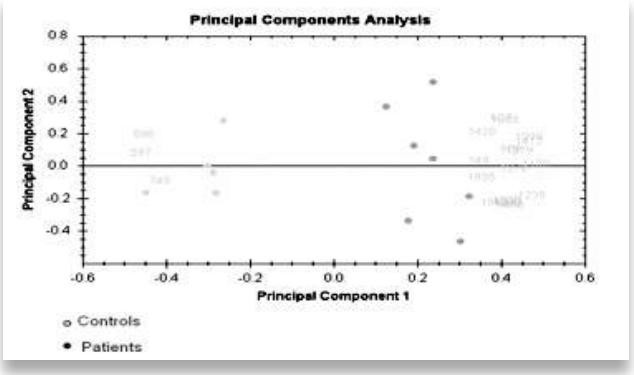


Figure 3B: Hierarchical cluster analysis using the expression patterns of 19 protein datasets that are differentially expressed between the control and patient samples.

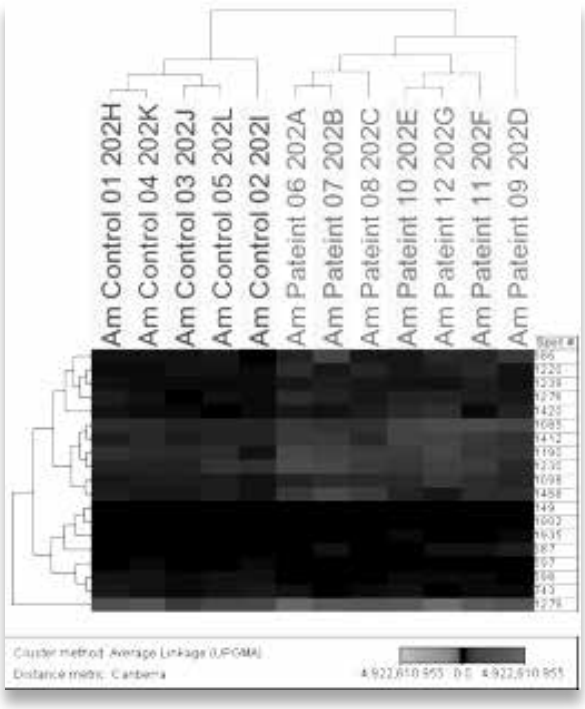
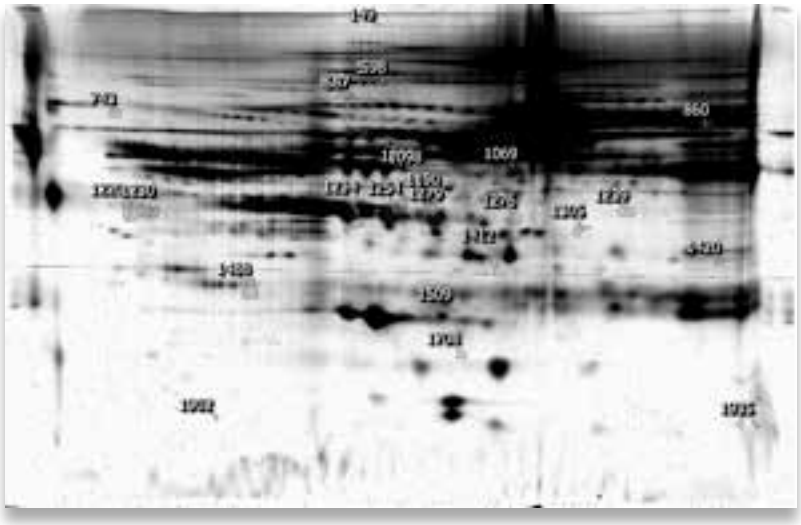


Figure 4: Representative 2 D gel image from a patient serum sample. Marked are gel distribution and location of differentially expressed spots between patient and control samples.



CONCLUSION

In summary, we have used 2-DE to separate proteins from serum samples of allergy patients exposed to different Amaranthus 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.

PUBLICATIONS

- WAQAR, M.A., HASNAIN, S.M, KHAM, M. (2010). Airborne pollen survey in Karachi: A coastal city in Sindh province of Pakistan. *Indian J. Aerobiol*., Volume 23, No. 1, pp. 7-17.
- HASNAIN, S.M., AL-SINI, H., AL-QASSIM, A. AL-FRAYH, A. ET AL (2010): "Protein Expression Profile of Indigenous and Commercial Extracts of Amaranthus Pollen in Allergy Patients". WAO International Scientific Conference, Dubai, UAE, 05-08 December 2010.

SUBMITTED MANUSCRIPT

- 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.*).
- HASNAIN, SM., KHAN, S., AL-QASSIM A., AL-FRAYH AR. Prevalence of Asthma, Allergic Rhinitis and Eczema in the Middle East and Neighboring Countries (*Allergy, European Journal of Allergy and Clinical Immunology*).
- HASNAIN, SM., KHAN, S., AL-FRAYH, AR., Allergenic Factors in Asthma and Allergy in the Middle East and Neighboring Countries (*Annals of Allergy*).

TECHNICAL REPORTS

- Isolation, purification and immunochemical characterization of allergenic protein(s) from *Amaranthus viridis* pollen grains. 4th Short Technical Progress Report. Submitted to KACST: ARP 27-11
- Isolation, purification and immunochemical characterization of allergenic protein(s) from *Amaranthus viridis* pollen grains. 5th Progress Report for the 1st Half of the Extended Period. Submitted to KACST: ARP 27-11.

ALLERGOTEK REPORTS

- Allergotek Diagnostic and Therapeutic Program Project Report No. 1
- Allergotek Diagnostic and Therapeutic Program Project Report No. 2
- Prevalence of Asthma in the World
- Prevalence of Asthma in Gulf Regions
- Sublingual Immunotherapy
- Specific Immunotherapy
- Death from Asthma

ABSTRACTS PUBLISHED

- HASNAIN, S.M., AL-SINI, H., AL-QASSIM, A. AL-FRAYH, A. ET AL (2010): "Protein Expression Profile of Indigenous and Commercial Extracts of Amaranthus Pollen in Allergy Patients". WAO International Scientific Conference, Dubai, UAE, 05-08 December 2010.

INVITED CHAIR INTERNATIONAL

- Invited to Chair session:"Allergen and risk factors", WAO International Scientific Conference in Dubai, UAE from 5-8 December 2010.
- Invited to Chair session:"Asthma and upper airway co-morbidities in the Gulf and near East", WAO International Scientific Conference in Dubai, UAE from 5-8 December 2010.

NEWSPAPER ARTICLE

- HASNAIN, SM (2010) Asthma, Allergy and Protection, Al-Riyadh Arabic Newspaper, 2010.

Breast Cancer Research

Head

Suad M. Bin Amer Al-Abdoullah , PhD

Member

Asmaa Nofal

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

RESEARCH PROJECTS

Project title

Identification of environmental and genetic factors that influence breast cancer development and therapy in Saudi females (RAC # 2031091-In collaboration with KACST).

Investigators: Suad Bint Mohamed Bin Amer, Dilek Colak, Taher Al-Tuweigeri, Asma Tulbah, Dahish Ajarim and Osama Almalik

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 aimed to study the potential that chemotherapy responses, specifically resistance may differ significantly between the Caucasians and Middle Eastern populations. The Affymetrix Genechip Human Genome U133 Plus 2.0 Array is being used to carry out the gene expression studies.

Project Progress

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

Genome- wide Gene Expression Analysis: We performed genome-wide gene expression profiling to characterize the underlying biological mechanisms of breast cancer in young women in Saudi Arabia. We analyzed the whole-genome mRNA expression profile from tumor and adjacent disease free tissues of 115 samples using Affymetrix GeneChip Human Genome U133 Plus 2.0 Arrays. We compared mRNA expression in tumors in young (≤ 45 years) (n=35) to those arising in two mature groups: 45 to 55 (n=13); and older age ≥ 55 (n=25). Within the young women's subset, additional analyses were performed comparing women age younger than 35 years (very young) with those age 35 to 45 years. Functional pathway, gene

Gene Category	List Hits	EASE score
embryogenesis and morphogenesis	7	1.18E-02
mitotic cell cycle	16	1.75E-02
cell cycle	27	2.36E-02
cell proliferation	37	2.63E-02
cation homeostasis	6	3.29E-02
DNA metabolism	21	4.03E-02
DNA replication and chromosome cycle	10	4.18E-02
ion homeostasis	6	4.54E-02
cell ion homeostasis	6	4.54E-02
cell death	17	4.61E-02
morphogenesis	35	4.66E-02
death	17	4.93E-02
M phase	9	5.00E-02
apoptosis	16	5.31E-02

Table 1: Gene Ontology categories overrepresented in up- or down-regulated in tumors in very young women compared to age-matched normal controls- GO categories that exist in significant abundance (EASE score < 0.05). The number of genes in respective GO categories is shown under "List hits" followed by the categories EASE score. An EASE score of < 0.05 indicates significance..

ontology and network analysis of tumor specific genes (up/down-regulated) were performed. Moreover, we also compared the gene expression profile characteristic of the sequential disease stages (DCIS and IDC) of breast cancer as well as age-matched normal controls within the young patients to discover genes specifically activated or inactivated during the course of breast cancer progression.

We have identified 77 signature genes specific to tumor in young age (≤ 45). A subset of differentially expressed genes was validated using real-time RT-PCR. In addition, selected signature genes were also confirmed by using immunohistochemical staining for young group vs. older group peri-menopause and post-menopause of Saudi breast cancer patients.

The enriched functional categories of young-age tumor signature genes include carcinogenesis, tissue development, cellular development, cellular growth and proliferation, tumor morphology, and cell death as shown in Table 1. Furthermore, we found that 143 genes differentially regulated between IDC and DCIS, 96% of which were down-regulated in IDC compared to DCIS. The network analysis revealed potential critical regulatory role of PI3K/Akt, NFκB, Jnk, and ERK pathways during progression from DCIS to IDC in younger women.

MAJOR FINDINGS OF THIS YEAR:

- The power of gene expression profiling is the ability to understand biology beyond what may be apparent from the study of clinical variables or individual gene markers.
- We identified genes and pathways specifically activated or inactivated during the course of breast cancer progression arising in young women.
- Our genomewide expression and network analysis indicated the dysregulation of DUSP6, PI3K and MAPK pathways; hence targeting these genes/pathways may have potential impact on the treatment of young Saudi breast cancer patients.
- 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 # 2030058 - In collaboration with Department of Cyclotron and Radiopharmaceuticals).

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

Project description

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

Status

This project has been completed in 2010.

Cell Biology Laboratory

Head

Futwan Al-Mohanna PhD. F.I.Biol. FRSC
Kate S Collison, PhD

Diabetes Research Staff
Soad Saleh
Angela Inglis
Nadine Makhool
Marya Zia (Grant)
Razan Bakheet
Rhea Mondreal (Grant)
Rana Al-Rabiah
Bernard Andres
Aziza Al Enazi
Rosemarie Ubungen (Grant)

Cardiovascular Research Staff
Ranjit Parhar, PhD
Reem Al-Hejailan
Mohammed Kunhi
Xing Zang Yang, MD
Qammar Al Haffar (Grant)
Peeyush Kumar (Locum)

The prevalence of overweight and obesity in Saudi population is 63%, and as of 2009, 30% of the population suffers from Type 2 Diabetes (T2D). Additionally, 60% of T2D patients suffer from cardiovascular disease. T2D is a multifactorial disease proceeded by hypertriglyceridemia, hyperglycemia, impaired glucose homeostasis and adiposity. Although there is a genetic element to T2D, the main determining factors relate to diet and lifestyle. 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 additives Monosodium Glutamate and Aspartame, both classified as excitotoxins.

The increasing burden of cardiovascular disease has prompted the search for solutions to the failing heart, when medication is no longer an option. Our research has focused on strategies to allogenize donor organs from other mammalian species. We are exploring the possibility of decellularizing donor hearts which could then be repopulated with human stem cells. Total number of publications this year: seven. Total amount of funding generated through these activities: SR 2,448,172.

PROJECTS

Project title

Role of Excitatory Amino Acids on Trans fat-induced Obesity, Dyslipidemia, Hepatic Steatosis and Cognitive Impairment (RAC 2092 028).

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

Progress

We found evidence for impairment of glucose homeostasis and spatial cognition in Aspartame-treated animals. The combination of Aspartame and Monosodium Glutamate showed more impairment in glucose homeostasis than Aspartame alone, suggesting that the effects of these excitotoxins are additive. Aspartame is rapidly metabolized into methanol, phenylalanine and aspartate. N-methyl D-aspartate (NMDA) receptors, which are concentrated in the central nervous system in areas which control energy balance (the hypothalamus) and learning (hippocampus), have binding sites for glutamate and aspartate. This may explain why the effects of Aspartame and Monosodium Glutamate appear to be additive. We have published 2 manuscripts this year and are preparing two further manuscripts for publication.

Project title

Metabolic Syndrome, Diabetes, and Cognitive Decline in a Feline Model (RAC# 2060 037).

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

Project description

Feline Diabetes closely resembles Human Type 2 Diabetes. Symptoms of the Metabolic Syndrome and markers of Insulin Resistance were induced in test subjects using specific Dietary manipulation of animals bred from female cats consuming the tested diets. Cognitive studies were performed towards the end of the study to assess working spatial learning and memory.

Progress

Metabolic deregulation, glucose and insulin homeostasis and hepatic steatosis was induced to varying degrees by the 3 dietary components. We used Affymetrix Mocroarray analysis to examine feline hepatic ggene regulation in response to diet. A manuscript concerning this is under consideration for publication.

Project title

Inflammatory Modulator protein Vaccinia Virus Complement Control Protein (VCP): Potential therapeutic in CVD (KACST BioTech Project 08-MED487-20).

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 HFCS-Induced Hepatic Steatosis: Expression Profiles in the Liver and Visceral Fat. Collison KS, Maqbool ZM, Inglis AL, Makhoul NJ, Saleh SM, Bakheet RH, Al-Johi MA, Al-Rabiah RK, Zaidi MZ, Al-Mohanna FA. *Obesity* (Silver Spring). 2010, 18(6):1122-34.
- 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 3;99(3):334-42.
- Effect of Trans fat, fructose and MSG feeding on feline weight gain, adiposity, Insulin sensitivity, adipokine and lipid profile. Collison KS, Zaidi MZ, Saleh S, Inglis A, Mondreal R, Makhoul N, Bakheet R, Milgram NW, Al-Mohanna FA. British *Journal of Nutrition*, 2011, 24:1-10.

DNA Repair and Apoptosis

Head

Abdelilah Aboussekhra, PhD

Members

Nisreen M. Al-Moghrabi, PhD
Mai Al-Mohanna, PhD
Bedri Karakas, PhD
Huda Al-Khalaf, PhD (Grant employee)
Siti-Faujiah Hendrayani, MSc (Grant employee)
Abeer Al-Qasem, Msc (Grant employee)
Ibtehaj S. Al-Sharif, BSc
Nujoud Al-Yousef, BSc

Cancer is a complex and heterogeneous genetic disease that results from the accumulation over age of a plethora of genetic and epigenetic alterations in various genes, which leads to uncontrolled cell proliferation and resistance to cell death. In addition, a higher order cell-cell interaction between cancer cells and their microenvironment is capital for tumor formation and spread. The major goals of this research section are to participate in understanding the fundamental processes of carcinogenesis, to elucidate the role of stromal cells in breast cancer onset and spread, and also the identification of novel natural anti-cancer molecules.

The major findings of this year are the following:

- The Atr protein kinase controls UV-dependent up-regulation of $p16^{INK4A}$ through inhibition of Skp2-related polyubiquitination/degradation.
- Shown that stromal fibroblast p16 has cell non-autonomous tumor suppressor function in breast cancer.
- Identification of Non-CpG and CpG cytosine methylation in the *BRCA1* promoter in peripheral blood cells from breast cancer-free females.
- Discovery of a novel anti-breast cancer molecule (PAC), with higher efficiency on ER-negative cells.

RESEARCH PROJECTS:

Project title

Investigation of the role of stromal fibroblasts in the development of breast carcinoma: The tumor suppressor $p16^{INK4A}$ protein as target (RAC # 2080009).

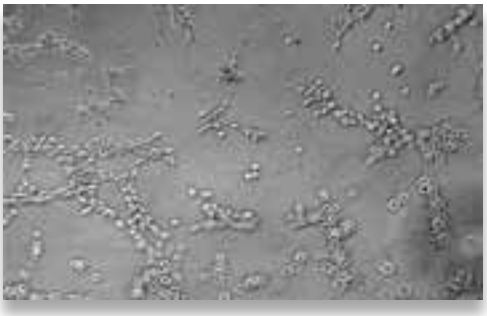
Investigators: A. Aboussekhra (PI), Mysoon Al-Ansary and Siti-Faujiah Hendrayani.

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

p16 down-regulation with specific siRNA activated breast fibroblasts, enhanced their migration/invasion and the phosphorylation of Erk and Akt and also increased the expression and secretion of SDF1, VEGF, IL-6 and MMP2. Consequently, media conditioned with these p16-deficient cells induced epithelial to mesenchymal transition and the migration/invasion of breast cancer cells, and endothelial cell differentiation into capillary-like structures (Figure 1).



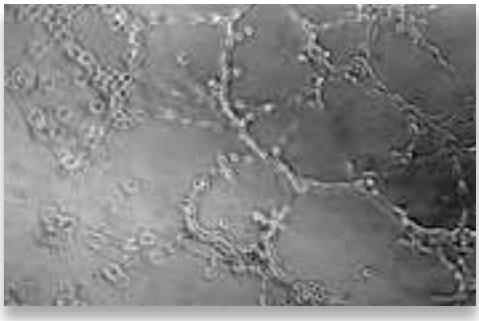


Figure 1. Serum-free conditioned media (SF-CM) from p16-siRNA expressing stromal fibroblasts (T64si-SFCM) activate HUVEC tube formation more than SF-CM from the control cells (T64C-SFCM).

Project title

Study of the role of tumor suppressor genes in DNA repair and cell cycle checkpoints (RAC # 990 025).

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

Project description

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

Progress

We have shown here that UVC up-regulates $p16^{INK4A}$ and the phosphorylated form of the protein at the 4 serine sites; Ser-7, Ser-8, Ser-140 and Ser-152. This accumulation of $p16^{INK4A}$ occurred through increasing the stability of both forms of the protein. Importantly, phospho-$p16^{INK4A}$ showed much higher stability, and UV treatment strongly increased its level in absence of *de novo* protein synthesis. Furthermore, we have shown that the UV-dependent up-regulation of both forms of $p16^{INK4A}$ is under the control of the protein kinase Atr, which suppresses their UVC-dependent proteasomal degradation. Interestingly, while this degradation is ubiquitin-related for $p16^{INK4A}$ through the Skp2 ubiquitin ligase protein, it is ubiquitin-independent for the phosphorylated form. In addition, we present clear evidence that Skp2 is up-regulated in *ATR*-deficient cells, leading to the down-regulation of the $p27^{Kip1}$ protein in response to UVC light. Moreover, we have shown a preferential association of endogeneous phospho-$p16^{INK4A}$

with Cdk4. This association increased following UV-treatment mainly for $p16^{INK4A}$ phosphorylated at Ser-140 and Ser-152. Besides, we have shown that Atr regulates UV-related p16/Cdk4-dependent and -independent phosphorylation of pRB and G1 cell cycle delay. Together, these results indicate that $p16^{INK4A}$ and $p27^{Kip1}$ are key targets in the Atr-dependent signaling pathway in response to the carcinogenic UV damage.

Project title

The methylation status of the BRCA promoter in Saudi breast cancer females (RAC # 2100011).

Investigators: Nisreen Al-Moghrabi (PI), Abeer al-Qasem and Abdelilah Aboussekhra

Project description

Breast cancer in Saudi Arabia is one of the most common malignancies and causes of death among women, and its incidence is increasing. The proportions of breast cancers that develop before the age of 40 represent 26.4% of all female breast cancers compared to 6.5% in USA. In the present project we aimed at investigating the epigenetic modification of the BRCA1 gene in breast cancer tissues and in blood cells derived from breast cancer and breast cancer-free Saudi females.

Progress

BRCA1 promoter methylation was detected in 13 primary sporadic breast cancer tissues (27.3%) and in 2 blood cells derived from breast cancer patients (28.5%). Intriguingly, *BRCA1* promoter was also methylated in blood cells from 8 breast cancer-free females (10.9%). Interestingly, a strong association was found between BRCA1 methylation and young age ≤40 at diagnosis (9/12) (75%) with a p-value of 0.0038. Furthermore, the median age at diagnosis of the patients with tumors harboring methylated *BRCA1* (38.5) and breast cancer-free females with methylated *BRCA1* in blood cells (32) was similar (*p=0.4363*). Moreover, we observed mutation-related methylation leading to the formation of methylated non-CpG, as well as the formation of novel methylated CpG sites in the 5' regulatory region of the *BRCA1* gene in the peripheral blood cells from cancer-free females (Figure 2).

Conclusions

The prevalence of *BRCA1* methylation is relatively high in the peripheral blood cells from breast cancer-free Saudi females. This suggests the possible implication of this process in the early onset of the disease and the potential use of this epigenetic modification as a powerful molecular marker for early detection.

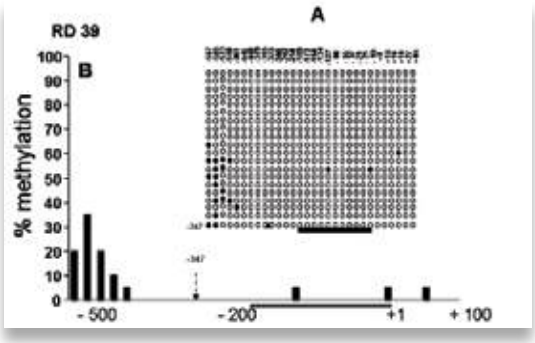


Figure 2. Cytosine methylation status of the BRCA1 CpG Island in the normal peripheral blood cells DNA samples. **(A)** Allelic patterns of cytosine methylation. **(B)** Graphical representations of the allelic patterns of cytosine methylation.

Project title

Study of the Anti-Cancer Properties of PAC (A Novel Curcumin Analogue) *in Vitro* and *In Vivo* (RAC # 2080027).

Investigators: A. Aboussekhra (PI), Ibrahim Al-Jammaz, Abeer Al-Qasem and Basem Al-Otaibi

Project description

We are aiming at investigating the anti-cancer effects of PAC on various cancer cell lines, and investigating the toxicity and the pharmacokinetics of this agent in rats. In addition, we would like to confirm the anti-cancer potential of PAC in vivo using tumor xenografts in mice. Our principal goal is to show that PAC could be of great value as anti-cancer agent, which will allow us, in the near future, to use this agent in phase 1 clinical trial in order to prove its safety and efficiency in humans.

Progress

PAC is 5 times more efficient than curcumin in inducing apoptosis, mainly via the internal mitochondrial route. This effect was 10 fold higher against ER-negative as compared to ER-positive cells, and ectopic expression of ERα rendered ER-negative breast cancer cells more resistant to PAC. Additionally, PAC delayed the cell cycle at G2/M phase with a stronger effect on ER-negative cells. Moreover, PAC exhibited strong capacity as an immuno-inducer through reducing the secretion of the two major Th2 cytokines IL-4 and IL-10 (Figure 3).

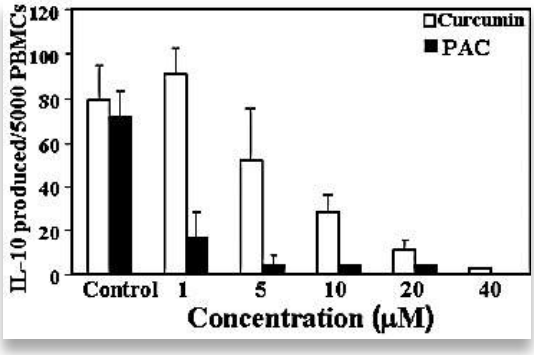


Figure 3. PAC is a strong suppressor of IL-10 expression.

Importantly, PAC significantly reduced tumour size, and triggered apoptosis *in vivo* (Figure 3). Furthermore, PAC inhibited survivin, NF-kB and its downstream effectors cyclin D1 and Bcl-2, and strongly up-regulated $p21^{WAF1}$ both *in vitro* and in tumours.

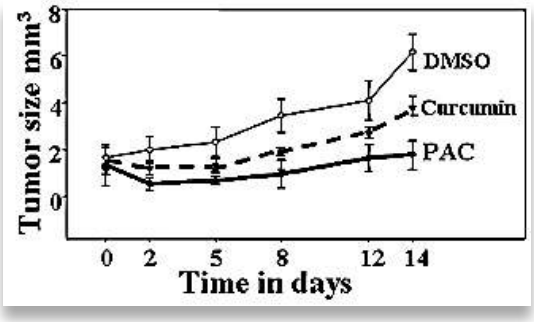


Figure 4. Anti-breast cancer effect of curcumin and PAC in nude mice.

Besides, PAC exhibited higher stability in blood and greater biodistribution and bioavailability than curcumin in mice.

Conclusions

PAC could constitute a powerful, yet not toxic, new chemotherapeutic agent against ER-negative breast tumours.

FUTURE RESEARCH DIRECTION

Further elucidate the molecular mechanisms that govern the functional interplay between breast carcinomas and their adjacent stromal fibroblasts and the role of the tumor suppressor p16 in this interaction. To this end, we will continue elucidating the mechanism of action of stromal p16 in suppressing breast cancer development. We are also interested in further studying the potential role of *BRCA1* methylation in predisposition and early onset of breast cancer in the Saudi females. Furthermore, we would like to further characterize the anti-cancer effects of PAC.

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- Abeer J. Al-Qasem, Mohamed Toulimat, Abdelmoneim M. Eldali, Asma Tulbah, Nujoud Al-yousef, Sooad K. Al-Daihan, Nada Al-Tassan, Taher Al-Tweigeri and Abdelilah Aboussekhra.TP53 genetic alterations in the Arab breast cancer patients: Novel mutations, pattern and distribution. (2011) *Oncology Letters* 2: 363-369.
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- Al-Hujaily EM, Mohamed AG, Al-Sharif I, Youssef KM, Manogaran PS, Al-Otaibi B, Al-Haza'a A, Al-Jammaz I, Al-Hussein K, Aboussekhra A. PAC, a novel curcumin analogue, has anti-breast cancer properties with higher efficiency on ER-negative cells. (2010) *Breast Cancer Res Treat*. Aug 1. [Epub ahead of print].
- Ghebeh H, Lehe C, Barhoush E, Al-Romaih K, Tulbah A, Al-Alwan M, Hendrayani SF, Manogaran P, Alaiya A, Al-Tweigeri T, Aboussekhra A, Dermime S. Doxorubicin downregulates cell surface B7-H1 expression and upregulates its nuclear expression in breast cancer cells: role of B7-H1 as an anti-apoptotic molecule. (2010). *Breast Cancer Res*. 2010;12(4):R48.
- 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 Al-Moghrabi, Abeer J. S. Al-Qasem and Abdelilah Aboussekhra. Non-CpG cytosine methylation of the *BRCA1* promoter in peripheral blood cells from breast cancer-free females. (2011). *International Journal of Oncology*. In press.

Environmental Health Section

Head

Iman Al-Saleh, PhD

Members

Neptune Shinwari
Ammar Al-Sabbahen
Reem Al-Rouqi
Rola Elkhatib
Cecilia Angela Obsum (until August 2010)

The Environmental Health Section (EHS) continues to maintain its primary goal to assess environmental pollutants that have a potential impact on the general population with a particular emphasis on children and women. During the 2010, we managed to complete our King Abdulaziz City for Science and Technology (KACST) funded project on phthalates and start preparing the logistic part of our newly KACST project "Mercury exposure during lactation and its effects on Saudi infant's neurodevelopment" which hopefully will start February 2011. We also offered training opportunities for four gifted students from King Abdulaziz Foundation Program and two graduate students from King Saud University. This report describes the progress of our ongoing projects, identifying 2010-2011 significant accomplishments and anticipated future directions.

ONGOING RESEARCH PROJECTS.

Project title

Saudi Children and mercury (Hg) exposure: the impact of dental amalgam (RAC# 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. Though the analytical part of this project was completed but the student is still working on data analysis and finalizing her master thesis.

Investigators: Iman Al-Saleh (principal investigator), Alanoud Al-Sudairi (a master student) and Ebtesam Al Olyan (co-investigator).

Project description

Mercury (Hg) 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

Initial data analysis showed that children with amalgam fillings (n=106) had significantly higher adjusted urinary Hg for creatinine (AUHg) levels than children without (n=76) with mean of 3.763µg/g Cr versus 3.457µg/g Cr respectively, P=0.019. The results were the same for unadjusted UHg in urine (P=0.01). Similar pattern was seen for hair mercury (HHg), and the mean was 0.614µg/g, n=97 for children with versus 0.242 µg/g (n=74) for those without amalgam fillings with P=0. Though the mean Hg in nail (NHg) was higher in children without amalgam (0.222 µg/g, n=61) versus those with (0.163 µg/g, n=101), the relationship was not significant (P=0.069). Graphical presentation of the results is shown in Figure 1. After adjusting for many confounders, the multiple logistic regression model revealed that the levels of UHg and HHg were 2.239 and 5.007 times respectively higher in children with dental amalgam compared to those without (P<0.01). In general, our study showed that significant number of children, whether with or without dental amalgam had Hg levels exceeding the acceptable reference limits. These results are alarming and there is an urgent need for carrying out more biomonitoring and exposure assessment studies. Changes in dental amalgam practices, especially for children are highly recommended in order to avoid unnecessary risk of Hg exposure.

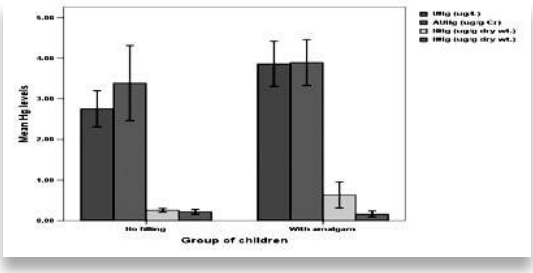


Figure 1. The levels of Hg in urine, hair and nail in children with and without dental amalgam. Error bars show mean + SE.

Project title

Determination of phthalates in drinking water, juices and milk packed in locally manufactured plastic bottles (RAC # 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. Though we submitted the final report to KACST on 13th of November 2010, we are still working on developing the methods for measuring milk and juice by using the Gas Chromatography/mass selective detector (GC/MSD) with the CombiPAL autosampler. One manuscript has already been submitted to peer-reviewed journal for publication.

Investigators: Iman Al-Saleh.

Project description

The wide availability of different brands of bottled water in Saudi markets which are packed in disposable plastic bottles led us to design this study in order to evaluate the extent

of the problem in highly consumed products. We used Gas Chromatography with the Mass spectrometer detector (GC/MSD) to determine phthalates in conjunction with solid-phase microextraction (SPME) using a 65 µm polyacrylate fiber. Dimethyl phthalate (DMP), diethylphthalate (DEP), di-*n*-butyl phthalate (DBP), benzyl butyl phthalate (BBP) and diethyl hexyl phthalate (DEHP) were measured in 10 brands of locally produced bottled water and stored under different conditions. Most of these phthalates were detected in selected bottled water as illustrated in Figure 2. Storage at 40C for 33 days exhibited the highest levels of various phthalate compounds. Though, the levels of phthalates in bottled water samples stored outdoor for 98 days were significantly higher than those stored at room temperature for 48 days, both were lower than phthalates found in those stored at 4°C as shown in Figure 3. It seems that phthalates in water did not leach from the plastic containers, but might be contaminants from the manufacturing process. Apart from DEHP (<6µg/L), there are not current legislations for other phthalates. Regardless of storage conditions, all our samples did not exceed the maximum established limit of DEHP. On the other hand, in most cases the levels of phthalates were above the method's detection limit. Although, our calculated RfD values were much less than the proposed RfD values for chronic oral exposure, we should consider the long term cumulative exposure to phthalates, especially to potentially vulnerable populations (infants and pregnant women We should not also rule out the possible synergistic toxic effects that might various phthalates in any matrix exhibit with metal and/or organic compounds. Saudi Arabia is number 12 in bottled water consumption (88 L per capita in 2004) among the 71 reported countries. With this high consumption, a quality assurance scheme for residue monitoring in water is quite important.

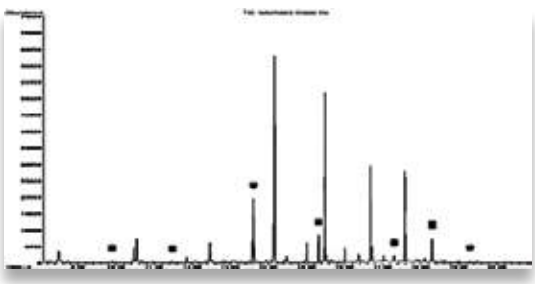


Figure 2. Examples of chromatogram obtained by the SPME–GC/MSD (SIM) analysis of phthalates extracted from two brands of bottled water sample.

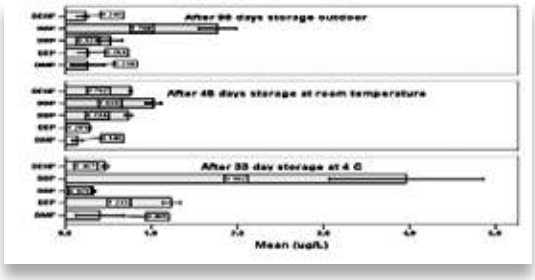


Figure 3. Concentrations of studied phthalates (µg/L) in bottled water under different storage conditions.

NEWLY FUNDED PROJECT

Project title

Mercury exposure during lactation and its effects on Saudi infant's neurodevelopment (RAC # 2080 049).

This project is funded by King Abdulaziz City for Science and Technology (KACST # ARP-29-23) with a total fund of SR 1,050,000. The project will be started on 14th February 2011 for 36 months.

Investigators: Iman Al-Saleh (principal investigator) and Michael Nester (co-investigator).

Project description

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

The main objectives of the study are: (1) to evaluate postnatal exposure to different forms of organic and inorganic mercury and its association with delayed neurological development at different age groups; (2) to identify a culturally relevant neurodevelopment assessment tool that can be used in a general practice settings; (3) to examine the extent of lactational transfer of mercury taking into account mercury speciation in order to have a critical assessment of its adverse health effects; (4) to test the role of oxidative stress due to mercury exposure on neurodevelopment defects in infants by measuring biomarkers such as urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) and malondialdehyde (MDA); (5) to compare different mercury exposure indicators in order to evaluate various forms of mercury exposure and their predictive validity for assessment of accurate biological monitoring. For example, blood and hair will be used to determine organic mercury, while urine is suitable to estimate elemental and inorganic mercury; (6) to identify sources of mercury exposure through the use of exposure-assessment questionnaires; and (7) to identify a cohort of infants with high levels of mercury for further studies in the future. This cross sectional study will recruit 1250 lactating Saudi mothers and their respective infants who have reached the ages of 3 to 12 months old during routine visits to their respective Primary Health Care Units in Riyadh. Different biological samples such blood, urine, hair and breast milk will be collected for mercury analyses using the Atomic Absorption Spectrophotometer, coupled to Vapor Generator Accessory. Infant developmental status will be assessed by the use of Denver Developmental Screening Test (DDST) which has four developmental dimensions: gross motor, fine motor-adaptive, language, and personal-social. The Parents' Evaluation of Developmental Status (PEDS) is another fast and inexpensive method for detecting developmental and behavioral-emotional problems will be also used which relies on parent's concerns about their infant's development. It is anticipated that this research project will provide relevant data to the public as well as health care community concerned with the impact of mercury on the health of young children especially with the recent concern over the use of thimerosal in vaccines and its possible association with autism and related disorders. Public health authorities could take the necessary legal and educational steps to restrict the availability of mercury containing products such as such as skin-lightening creams, thimerosal and dental amalgam.

FUTURE RESEARCH DIRECTION

- Identify our research priorities in the light of the rising national and international environmental issues;
- Continue to collaborate productively with our clinical colleagues in order to promote public awareness of the implications of our research findings for improved clinical management;
- Continue to publish brochures and articles about important topics to raise public health awareness regarding the environment; &
- Develop a fee-for-service program utilizing the existing human and technical expertise and resources.

PUBLICATIONS

- Al-Saleh I, El-Doush I, Arif J, Coskun S, Billedo G, Jaroudi K, Al-Shahrani A, Mohamed G. DNA adducts in the blood and follicular fluid of women undergoing in-vitro fertilization treatment and its effect on the outcome. *Bulletin of Environmental Contamination & Toxicology* 2010; 84(1): 23-28.
- Al-Saleh I, El-Doush I, Billedo G, Coskun S. Caffeine consumption in women undergoing *in-vitro* fertilization treatment and its effect on the IVF outcome. *Medical Science Monitor* 2010; 16(12):CR598-605.
- Al-Saleh I, N Shinwari, A Rabbah. In utero exposure to mercury (Hg) and its adverse effects on birth outcomes. *Toxicologist* 2010; 114: 390-391.
- Al-Saleh I, Mashhour A, Shinwari N, Mohamed G, Rabah A. Maternal and newborn heavy metal status in healthy women: Birth outcome study. In Press, Corrected Proof, Available online since 18 November 2010- *International Journal of Hygiene & Environmental Health*.

Molecular Virology and Infectious Diseases

Head
Ahmed A. S. Al-Qahtani, PhD

Members
Mohammed N. Al-Ahdal, PhD
Alwaleed Alaidan, PhD
Damian Dela Cruz, DVM
Suhair Abu-Zaid, MSc,
Marie Fe Bohol, BS
Mashael al-Enazi
Nisreen Khalaf
Hanan Shaarawi (Secretary)

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

SPECIAL ACCOMPLISHMENTS:

- Senior Editorship of the Journal of Infection in Developing Countries (Mohammed N. Al-Ahdal, PhD).
- Editorship of the Annals of Saudi Medicine (Mohammed N. Al-Ahdal, PhD).
- Advisory Board of the Saudi Pharmaceutical Journal (Mohammed N. Al-Ahdal, PhD).
- Board membership of the Saudi Society of Clinical Laboratory Sciences (Mohammed N. Al-Ahdal, PhD).
- DNA fringerprinting for tracing nosocmial pathogens in our hospital and other hospitals inside and outside Riyadh.
- One full proposal was presented to The National Comprehensive Plan for Science and Technology (NCPST) for fund for year 2011 as follows:
  Title: Complete hepatitis B virus genome sequence from Saudi patients with hepatocellular carcinoma.
  Proposed fund: 1,692,000 Saudi Riyals.
  Principal Investigator: Ahmed Al-Qahtani, PhD (MVID).
  Co-Investigators: Mohammed Al-Ahdal, PhD (MVID), Ayman Abdo,MD, (KSU), Faisal Sanai, MD (NGH), Hamad Al-Ashgar, MD (KFSHRC).
- We are collaborating with colleagues from King Khalid University, Abha, Saudi Arabia and a one full proposal was presented to KACST for fund for year 2011 as follows:
  Title: Epidemiology of cutaneous leishmaniasis in Assir region.
  Proposed fund: 1,500,000 Saudi Riyals.
  Principal Investigator: Saad Bin Dajem, King Khalid University, Abha, Saudi Arabia.
  Co-Investigatores: Ahmed Al-Qahtani, PhD (MVID), Mohammed Al-Ahdal, PhD (MVID),
- Approval of one project submitted to KACST.
  Title: Analysis of genomic variability of Hepatitis C Virus (HCV) and its role in resistance to treatment.
  Budget approved: 1,440,000.
  Principal Investigator: Ahmed Al-Qahtani (MVID),
  Co-investigators: Mohammed N. Al-Ahdal (MVID), Faisal Sanai, MD (National Guard Hospital), Ayman Abdo, MD (KSU), Hanif Khalak (RC Genetics Department).
- Approval of one project submitted to KACST.
  Title: Association of genetic variations with cutaneous leishmaniasis in Saudi patients.
  Budget approved: 840,000 SAR
  Principal Investigator: Saad M. Bin Dajem (King Khalid University, Abha),
  Co-investigators: Ahmed Al-Qahtani (MVID), Mohammed N. Al-Ahdal (MVID), Hanif Khalak (RC Genetics Department)
  Collaborate with various Saudi Universities in supervision of graduate students.

RESEARCH PROJECTS

Project title

Molecular fingerprinting of *Enterococcus faecium* clinical isolates and identification of genes conferring vancomycin resistance.

Investigators: Mohammed N. Al-Ahdal, Suhair M. Abuzaid, Haifa F. Al-Shammary, Marie F. Bohol, and Ahmed A. Al-Qahtani.

Project description

Vancomycin-resistant *Enterococcus faecium* is among the important nosocomial pathogens. Little is known about the characteristics of these bacteria in Saudi Arabia. Aside from the more abundant *Enterococcus faecalis*, 29 clinical isolates were identified in our institution as *E. faecium* from January 2009 until April 2010. All were ampicillin-, ciprofloxacin- and vancomycin-resistant (MIC >=32 µg/ml, microdilution method), some (9/29) were teicoplanin-resistant, and all were linezolid- and synercid-sensitive. PCR was performed to examine several

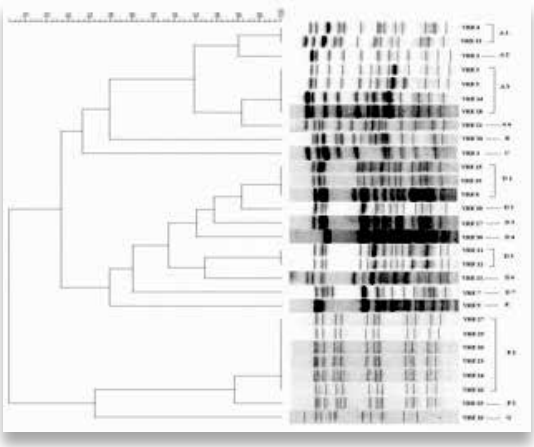


Figure 1. Pulsed-field gel electrophoresis of 29 Enterococcus faecium clinical isolates.

genes of vancomycin resistance and virulence factors. *VanA* gene was found in all isolates, while *VanB* was found in some (12/29) and *VanC* and its subtypes (*VanC1, VanC2, and VanC3*) were never found. Pulsed-field gel electrophoresis of the isolates showed 7 groups (A-G) based on 85% similarity, with most of the 12 *VanB*-positive isolates in the last 3 groups. Compared to isolates from around the world, it seems that our isolates are more susceptible to teicoplanin.

Project title

Molecular detection of genes conferring virulence of the vancomycine-resistant Enterococcus faecium clinical isolates.

Investigators: Mohammed N. Al-Ahdal, Suhair M. Abuzaid, and Ahmed A. Al-Qahtani.

Project description

Presence of genes producing protein that are considered virulence factors in the vancomycine-resistant *Enterococcus faecium* (gelatinase, eterococcal surface protein, adherence, cytolysin, and surface antigen) were also investigated by PCR using different primers. All isolates were positive for the gelatinase (gelE) and the enterococcal surface protein (esp) genes, but negative for the adherence (aggregation substance) genes (ace, asa1) and the cytolysin genes (cylA, cylL). The majority of the isolates were negative for the surface antigen (EF) gene. Compared to isolates from around the world, it seems that our isolates are less virulent.

Table 1. Virulence genes found in our *Enterococcus faecium* clinical isolates.

Number of samples positive for each virulence gene						
gelE	*esp*	*ace*	*asa1*	*cylA*	*cylL*	*EF*
29/29	29/29	0/29	0/29	0/29	0/29	12/29

Project title

Prevailing genotypes of hepatitis C virus in Saudi Arabia studied

through Meta analysis.

Investigators: Suhair M. Abuzaid, Mohamed M. Shoukri, Ahmed A. Al-Qahtani, and Mohammed N. Al-Ahdal.

Project description

Hepatitis C virus (HCV) infection is documented globally, but the genotype distribution in various geographical areas is not conclusive, although genotype 4 has been reported to be prevalent in the Middle East. We performed a meta-analysis on available literature on this issue from 1995 to 2011 in an attempt to confirm the prevailing HCV genotype in Saudi Arabia. Search of the literature for papers describing genotypes in Saudi Arabia was carried out. Meta analysis was performed on the samples in 18 studies, in which HCV genotypes were identified. A total of 2277 specimens from HCV-positive patients with genotype identification was found. No HCV genotyping studies were found previous to 1995. Our Meta analysis is in agreement with published data, showing that HCV genotype 4 is the most prevalent, followed by genotype 1. Further studies on subtype distribution are warranted.

Table 2. Confidence limit (95%) on combined estimates of prevalence based on the random effects model.

Limits	HCV1	HCV2	HCV3	HCV4
Lower	0.22	0.01	0.02	0.43
Upper	0.36	0.11	0.20	0.59
p-value	<.0001	<.0001	<.0001	<.0001

Project title

Genoprevalence of human papillomavirus in cervical specimens: A community study in Riyadh (RAC # 2091081).

Investigators: Mohammed N. Al-Ahdal, Walaa Al-Arnoos, Suhair M. Abuzaid, Marie F. Bohol, Mohamed M. Shoukri, Kamal El Rady, and Ahmed A. Al-Qahtani.

Project description

Human papillomavirus (HPV) has been implicated in silent cervical infections that may lead to cervical hyperplasia and cancer among women. In this study, the community prevalence of HPV infections among women is investigated. Endocervical specimen from each woman was taken. DNA from cells in the specimens will be extracted and subjected to amplification by the polymerase chain reaction (PCR) procedure, using HPV consensus primers which will detect the presence of any HPV (MY09/MY11 primers and the GP5/GP6 primers). PCR products

positive for HPV are being subjected to DNA hybridization using probes specific for each of the important LR-HPV genotypes (6 and 11) and HR-HPV genotypes (16, 18, 31, 33, 35, 45, and 50). Demographic data are being compiled through a questionnaire. Relationship between HPV positivity and demographic data will be analyzed through statistical packages. As no community study of HPV prevalence has ever been performed in the country (and in the capital city of Riyadh in particular), this project would be a first of its kind and will contribute to the global knowledge about the occurrence this sexually-transmitted agent. It will also alert the proper authorities of the prevalence of the disease and assist in the decision to recommend the HPV vaccine. PCR amplification of HPV was carried out on 519 specimens, of which 164 were HPV-positive. Currently these positive samples are being genotyped.

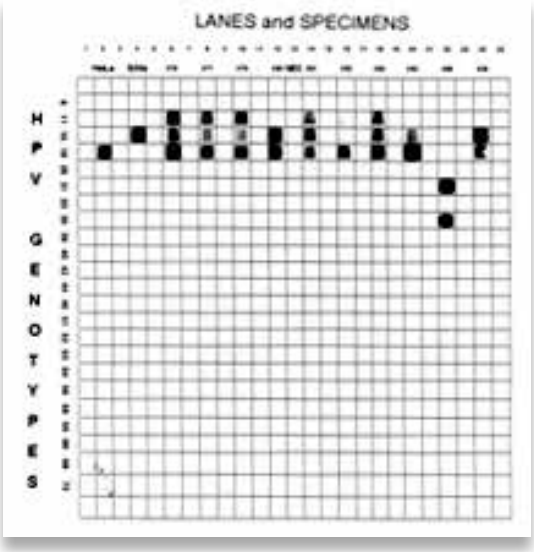


Figure 2. Reverse blot hybridization of some HPV-positive samples. Lane 2 is a positive control for HPV-18. Lane 4 is a positive control for HPV-16. Odd-numbered lanes are all negative controls. Lanes 6, 8, 10, 14, 16, and 18 are samples that show mixed HPV genotypes of 11, 16 and 18. Lanes 12, 20 and 24 show mixed HPV genotypes of 16 and 18. Lane 22 shows mixed HPV genotypes 31 and 35.

Project title

Sub-typing of genotype 4 of Hepatitis C Virus (HCV) and its relationship to disease progression (RAC project # 2060040).

Investigators: Ahmed A. Al-Qahtani, PhD (MVID), Damian Dela Cruz (MVID), Nisreen Khalaf, Mohammed N. Al-Ahdal, PhD (MVID).

Project description

Hepatitis C virus (HCV) is divided into several genotypes. The role of the genotype in disease progression is highly debated. Genotype 4 is the most predominant in Saudi Arabia followed by genotype 1. Here, HCV was sub-genotyped by sequencing of part of NS5B gene. The DNA sequence was analyzed by phylogenetic analysis against published sequences. Also, patients were classified according to disease characteristics as patients with chronic disease (n=196), liver cirrhosis (n=87) and hepatocellular carcinoma (HCC) (n=37). Phylogenetic analysis revealed that 81.94% (n=254) are genotype 4 and 18.06% (n=56) are genotype 1. Among genotype 4 carriers, 4a is the most dominant (47.24%, n=120) followed by 4d (42.91%, n=109). While of genotype 1, sub-genotype 1b is the most common (64.29%. n=36) followed by 1a (30.36%. n=17). There was significant distribution of subtype 4a in HCC subject (p value: 0016). In conclusion, the results indicate that sub-genotype 4a is the most predominant in Saudi Arabia and significantly associated with HCC. These results warrant that more samples are required to substantiate these results.

Project title

Sequence variations in the X gene of HBV and its role in the development of Hepatocellular Carcinoma (RAC project # 2060040).

Investigators: Ahmed Al-Qahtani, PhD (MVID), Damian Dela Cruz (MVID) Faisal Sanai, MD (National Guard Hospital), Ayman Abdo, MD (KSU), Mohammed Al-Ahdal, PhD (MVID).

Project description

Viral hepatitis caused by Hepatitis B Virus (HBV) is presented with different manifestations in infected individuals ranging from acute, to chronic disease. Small percentage of chronically infected individuals develop liver complications including liver cirrhosis and hepatocellular carcinoma (HCC). HBV is among the smallest known DNA viruses with a genome of approximately 3200 base pairs (bp). The exact genome size is genotype dependent and is reported to vary from 3182 to 3248 bp. The X antigen of HBV (HBx) is a trans-activator protein that is involved in regulation of virus gene expression and replication through the activation of the virus enhancer and promoter complexes. Such trans-activation activity is hypothesized to contribute to the persistence and progression of diseases associated with HBV. Here, we studied the natural mutations in X gene in 247 patient samples. Patients were

divided according to the disease status as follows; 107 inactive carriers, 78 active carriers, 37 cirrhosis and 25 HCC. Mutations affecting six codons at positions 5, 38, 94, 127,130, and 131 were found. We found mutations at positions 94 and 131 are found more frequently in patients with HCC than other patients. In conclusion, our results suggest that mutations in the X region could contribute to the development of HCC in HBV-infected patients.

Project title

Detecting mutations in PfCRT and PfMDR1 genes among Plasmodium falciparum isolates from Saudi Arabia by pyrosequencing.

Investigators: Saad M. Bin Dajem (King Khalid University, ABHA), Adel Ali H. Al-Sheikh (MOH, Jazan), Marie Fe Bohol (MVID), Mohammad Alhawi (King AbdulAziz University, Jeddah) Mohammed N. Al Ahdal (MVID), Ahmed Al-Qahtani (MVID)

Project description

The emergence of chloroquine resistance in Plasmodium falciparum is a significant public health problem where malaria is endemic. We aimed to evaluate the efficacy of pyrosequencing to assess chloroquine resistance among P. falciparum isolates from the southwestern region of Saudi Arabia by analyzing the K76T and N86Y mutations in the P. falciparum chloroquine resistance transporter (PfCRT) and P. falciparum multidrug resistance 1 (PfMDR1) genes, respectively. Blood samples (n=121) from microscopically positive P. falciparum cases were collected. DNA was extracted, and fragments from each of the genes were amplified by PCR using new sets of primers. The amplicons were sequenced using a pyrosequencer. All of the 121 samples were amplified for assessment of the PfCRT K76T and PfMDR1 N86Y mutations. All of the samples amplified for the PfCRT 76T mutation harbored the ACA codon (121/121; 100%), indicating the presence of the 76T mutation. For the PfMDR1 N86Y mutation, 72/121 samples (59.5%) had the sequence AAT at that position, indicating the presence of the wild-type allele (86N). However, 49/121 samples (40.5%) had a TAT codon, indicating the mutant allele (Y) at position 86. This study shows that pyrosequencing could be useful as a high throughput, rapid, and sensitive assay for the detection of specific single nucleotide polymorphisms in drug-resistant P. falciparum strains. This will help health authorities in malaria-endemic regions to adopt new malaria control strategies that will be applicable for diagnostic and drug resistance assays for malaria and other life-threatening pathogens that are endemic in their respective.

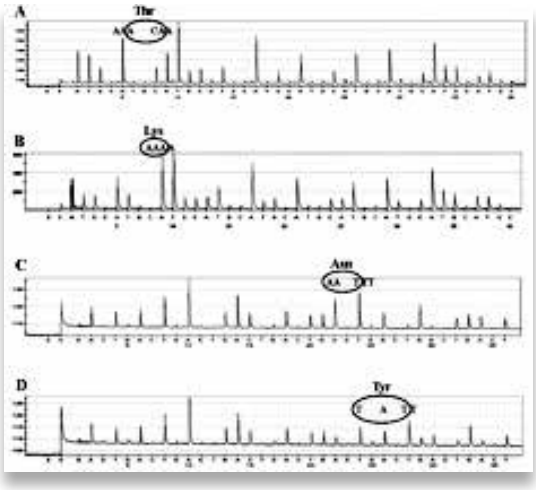


Figure 3. Sample pyrograms generated from a PSQ 96MA. Pyrograms that show the peak profiles for PfCRT mutant 76T (**a**) and the PfCRT wild-type 76K (**b**). Pyrograms showing the peak profiles for wild-type asparagine (**c**) and mutant tyrosine (**d**) alleles at position 86 of PfMDR1. The nucleotide added at each step is indicated at the bottom of the program.

Project title

Toll-like receptor 3 polymorphism and its association with Hepatitis B Virus infection in Saudi patients (RAC project # 2060040).

Investigators: Ahmed Al-Qahtani (MVID), Mohammed Al-Ahdal (MVID), Ayman Abdo (KSU), Faisal Sanai (NGH), Mashael Al-Anazi (MVID), Nisreen Khalaf (MVID), Saud Al-Arifi (KSU), Majid Al-Okail (KSU), Hamad Al-Ashgar (KSU), Khalid Al-Kahtani (KFSHRC), Hind Al-Humaidan (KFSHRC), Riham Al-Swayeh (KFSHRC), Fahad Al-Majhdi (KSU).

Project description

Individuals infected with HBV show a wide spectrum of disease manifestation ranging from asymptomatic carriers to hepatocellular carcinoma HCC. The host immune mechanism is the most important determinant of liver injury in HBV-infected patients. TLR3 is part of the innate immune system and it recognizes double stranded RNA (dsRNA) and provides early immune response to exogenous antigen. Genetic polymorphism in TLR3 is considered to be an important factor for the susceptibility to certain viral pathogens including hepatitis B virus. Due to lack of knowledge on the role of TLR3

polymorphisms in HBV-infected individuals, we investigated the distribution of nine single nucleotide polymorphisms (SNPs) in TLR3 in Saudi patients infected with HBV. A total of 707 HBV-infected patients and 570 uninfected controls were examined for different parameters including SNPs (rs5743311, rs5743312, rs111611328, rs1879026, rs5743313, rs5743314, rs5743315, rs78726532, and a newly identified SNP located at position 184322913 of chromosome 4). The HBV infected patients were predominantly of genotype D (88.5%), genotype A, B and E constitute 8% while mixed genotypes were approximately 4%. The sequence analysis confirmed that only one SNP rs1879026 (G/T), showed significant difference (P= 0.048); odds ratio (OR), 3.726; 95% confidence interval (CI), 1.856-7.480) in the distribution between HBV carriers and uninfected controls. No significant association was found among other SNPs except that two SNPs (rs78726532 and rs5743315) were very close the border line. Our findings indicate that SNP rs1879026 (G/T) of TLR3 is prevalent in HBV Saudi population and warrants further analysis with regard to disease severity.

Table 3. Distribution of genotype/alleles in the control subjects, inactive subjects, active subjects, cirrhosis with HCC subjects.

SNPs	Genotype/ alleles	Control (n=570)	Group I Inactive (n=441)	Group 2 Active (n=190)	Group 3 Cirrhosis (n=55)	Group 4 Cirrhosis + HCC (n=21)	X2	P value
rs1879026	GG	416	324	140	38	17	4.560*	0.102*
	GT	160	108	46	13	4	1.981#	0.371#
	TT	23	8	4	4	0	4.224•	0.121•
	G	992	756	326	89	38	3.660*	0.056*
	T	206	124	54	21	4	1.868#	0.172#
							3.896•	0.048•

*: control vs case 1 #: control vs case 2; •: control vs case 1 plus case 2 plus case3 plus case 4; case 1: inactive subjects; case 2: active subjects; case 3: cirrhosis subjects; case 4: cirrhosis with HCC subjects.

Project title

Association of RANTES gene polymorphisms with hepatitis B virus infection in Saudi population (RAC project # 2060040).

Investigators: Mohammed N Al-Ahdal (MVID), Ahmed Al-Qahtani (MVID), Ayman Abdo (KSU), Faisal Sanai (NGH), Mashael Al-Anazi (MVID), Nisreen Khalaf (MVID), Saud Al-Arifi (KSU), Majid Al-Okail (KSU), Hamad Al-Ashgar (KFSHRC), Hind Al-Humaidan (KFSHRC), Fahad Al-Majhadi (KSU)

Project description

Besides host immune response, genetic and environmental factors play crucial role in the manifestation of Hepatitis B virus (HBV) infection. Regulated on activation normal T cell expressed and secreted (RANTES) plays a vital role in CD4+, CD8+ T-lymphocyte and dendritic cell activation and proliferation in the inflammation. Single nucleotide polymorphisms (SNPs) in RANTES gene are associated with several viral and non viral diseases. Although are limited, association studies have invariably indicated the lack of association between RANTES gene SNPs and HBV infection in several ethnic populations. The RANTES gene SNPs exhibit distinct ethnic distributions. Despite the high prevalence of HBV infections in Saudi Arabia no studies were carried out relating the RANTES gene polymorphisms with the disease susceptibility and progression. Here we tested the association of -403G> A, and -28C> G RANTES gene variants to HBV infection in 473 healthy control and 484 HBV patient Saudi ethnic populations. Significant differences were found in the genotype and allele distributions of studied SNPs between the control and the HBV patients. Both the SNPs were significantly linked to viral clearance in these subjects. Our data demonstrate for the first time in a Saudi population, a relationship between the RNATES gene polymorphisms and the clinical course of HBV infection and underscore the importance of evaluating the genetic background of the affected individual while ascertaining the disease progression.

Table 4. Single marker association tests on chromosome 3 in active subjects and in cirrhosis plus cirrhosis with HCC subjects.

SNP	Assoc Allele	Case, Control Ratios counts	Case, Control Ratios frquencies	Chi Square	P value
rs1799864	A	18:112, 92:664	0.138, 0.122	0.287	0.5923
rs1799987	A	55:85, 274:528	0.393, 0.342	1.375	0.2409
rs1800023	A	85:55, 447:355	0.607, 0.557	1.202	0.2729
rs1800024	T	34:106, 108:692	0.243, 0.135	10.808	0.001
rs3204849	A	62:62, 368:372	0.500, 0.497	0.003	0.9556
rs6441977	A	7:117, 25:715	0.056, 0.034	1.53	0.2161

PUBLICATIONS (2010)

- Al-Qahtani AA, Kessie G, Dela Cruz DM, Al-Faleh FZ, Al-Ahdal MN (2010) Quasispecies of genotype 4 of hepatitis C virus genomes in Saudi patients managed with interferon alpha and ribavirin therapy. *Annals of Saudi Medicine* 30:109-114.
- Tayeb HT, Al-Ahdal MN, Carter MJ, Al-Qahtani A, Dela Cruz DM (2010) Molecular epidemiology of human astrovirus infections in Saudi Arabia pediatric patients. *Journal of Medical Virology* 82:2038-2042.
- Al-Qahtani A, Al-Hazzani T, Al-hussain T, Al-Ghamdi A, Al-Mana H, Al-Arifi S, Al-Ahdal M, Aly M. (2010). Correlation between clinical characteristics, survival and genetic alterations in patients with hepatocellular carcinoma from Saudi Arabia. *Cancer Genet Cytogenet*. 203(2):269-77.
- Colak D, Chishti MA, Al-Bakheet AB, Al-Qahtani A, Shoukri MM, Goyns MH, Ozand PT, Quackenbush J, Park BH, Kaya N. (2010). Integrative and comparative genomics analysis of early hepatocellular carcinoma differentiated from liver regeneration in young and old. *Mol Cancer*. 12;9:146.
- Bin Dajem SM, Al-Sheikh AA, Bohol MF, Alhawi M, Al-Ahdal MN, Al-Qahtani A. (2011). Detecting mutations in PfCRT and PfMDR1 genes among Plasmodium falciparum isolates from Saudi Arabia by pyrosequencing. *Parasitol Res*. 2011 Feb 25. [Epub ahead of print].
- Meo SA, Assad AA, Sanie FM, Baksh ND, Al-Qahtani A, Shaikh ZA. (2010). Transmission of hepatitis-B virus through salivary blood group antigens in saliva. *J Coll Physicians Surg*. 20(7):444-8.
- Bin Dajem SM, Mostafa OM, Abdoon A, Al-Quraishy SA, Al-Qahtani AA. (2010). Isoenzyme electrophetic characterization of Leishmania major, the causative agent of zoonotic cutaneous Leishmaniasis in North and West Saudi Arabia. *J Egypt Soc Parasitol*. 40(2):465-78.
- Faisal M Sanai, Ahmed Helmy, Khalid I Bzeizi, Mohammed A Babatin, Ahmed Al-Qahtani, Hamad A Al-Ashgar, Abdallah S Al-Mdani, Ahmad Al-Akwaa, Souad Almutharea, Mohammed Q Khan, Abdullah S Alghamdi, Taha Farah, Haziz Al-Biladi, Waleed Al-Hamoudi, Mayssa Saadeh, Ayman A Abdo. (2011). Discriminant Value of Serum HBV DNA Levels as Predictors of Liver Fibrosis in Chronic Hepatitis B. *J viral Hep*. Accepted.
- Al-Qahtani AA, Rubino S, Al-Ahdal MN. (2011). Sequence variation of the HVR1 region of Hepatitis C virus in response to interferon-α and ribavirin treatment. *Journal of Infection in Developing Countries*. Submitted.

ABSTRACTS

The following abstracts were submitted to:

XV, International Congress of Virology. 11-16 September 2011. Organized by the International Union of Microbiological Societies Meeting (IUMS, 2011, Sapporo, Japan)

- Toll-like receptor 3 polymorphism and its association with hepatitis B virus infection in Saudi patients. Ahmed Al-Qahtani, Mohammed Al-Ahdal, Ayman Abdo, Faisal Sanai, Mashael Al-Anazi, Nisreen Khalaf, Saud Al-Arifi, Majid Al-Okail, Hamad Al-Ashgar, Khalid Al-Kahtani, Hind Al-Humaidan, Riham Al-Swayeh, Fahad Al-Majhdi.
- RANTES gene polymorphisms (-403G> A, and -28C> G) and hepatitis B virus infection in a Saudi population. Ahmed Al-Qahtani, Mohammed Al-Ahdal, Ayman Abdo, Faisal Sanai, Mashael Al-Anazi, Nisreen Khalaf, Saud Al-Arifi, Majid Al-Okail, Hamad Al-Ashgar, Hind Al-Humaidan, Fahad Al-Majhdi.

The following abstract was submitted to:

49th meeting of Infectious Diseases Society of America (IDSA). October 20-23, 2011, Boston, MA, USA.

- Characterization of Vancomycin-Resistant Enterococcus faecium Isolates from Saudi Arabia. Mohammed Al-Ahdal, Suhair Abuzaid, Haifa Al-Shammary, Marie Bohol, and Ahmed Al-Qahtani

Tuberculosis research Unit

Head
Sahal Al-Hajoj, PhD

Members
Bright Varghese
Ruba Al-Omari
Mais Al-Herbawi
Raniya Abdullah

According to the estimate 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.

RESEARCH PROJECTS

Project title

Epidemiology of drug resistance TB in Saudi Arabia (KACST approved grant).

Investigators: Sahal Al-Hajoj, PhD, Fahad Al-Raabiah, Zyad Memish, Sahar Al-Thwadi and Nalea AboulJadeal

Project description

The purpose of this project is to study the drug resistance level in the country.

Progress

More than 3000 isolates were collected from 9 regions in the country. DST was carried out for all of the isolates. Data being analyzed.

Project title

Detection of Interferon gamma Production for the Diagnosis of Latent Tuberculosis in Patients for Kidney Transplantation

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

Project description

This project will focus on detection of dormant tuberculosis in a very veruable group of patients. Usually the routine work out for patients undergo renal transplantations is including 100 year ancient skin test which some times give controversial results and on other occasion does not even detect dormant TB as a results of its low sensitivity.

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

Progress

This project has been finally approved by Research Advisory Council (RAC) 200 blood samples have been received so far. All the samples were tested for interferon gamma. It is expected to execute this project within the coming 12 months as we still need to recruit on the 100 patients.

Data base with collaboration of BSECS has been created under the name of Tuberculosis database. It is available on the web site.

PRESENTATION

1. Bright Varghese, Mais Herbawi, Ruba Al-Omari, Ranya Abdullah, Sahal Al-Hajoj: Poster: "Drug Resistance Survilleance and its Effect on NTP". European Society of Mycobacteriology (ESM). Bled, Slovenia, 3-7 July 2010.

PUPLICATIONS

- Sahal A. M. Al-Hajoj et al: Microevolution of Mycobacterium Tuberculosis in Tuberculosis Patient: *Journal of Clinical Microbilogy*. August 2010.
- Sahal A.M. Al-Hajoj1, Nalin Rastogi3: "The Emergence of Beijing Genotype of Mycobacterium Tuberculosis in the Kingdom of Saudi Arabia". *Annals of Thoracic Medcine*; Vol 5, Issue 3, July-September 2010.

SUBMITTED PROJECTS

2. Evaluation of QuantiFERON-TB in patients with Extrapulmonary Tuberculosis. Submitted to ORA.
3. Genotyping Mycobacterium Tuberculosis from patients with Extrapulmonary Tuberculossis". Submitted to ORA.
4. Detection of Interferon Gamma Proudction for the diagnosis of Latent Tuberculosis in health care workers at King Faisal Specialist Hospital and Research Centre. Submitted to ORA.
5. Investigation of local pilgrims (5000 individuals) before they leave for Hajj, and the 3 months on their return". The purpose of this project is to see the prevalence of TB among local pilgrims whom got the infection during Hajj. Of course the ultimate aim.
6. Epidemiology and Genetic Diversity of Non-Tuberculosis Mycobacteria in Saudi Arabia: submitted to ORA and Biotechnology program.
7. Epidemiology of Childhood Tuberculosis in Saudi Arabia: Genetic Diversity and Existence of Drug Resistance submitted to ORA and Biotechnology program.

TRAINING AND EDUCATION

In July 2010 I completed supervising fully a Master student (June 2010 – July 2010). Dian Ruchma, from King Saud University. My role was to give her graduation projects and supervise her as she executed these projects. As it can be seen, I can teach the following subjects with ease of confidence

INTERNATIONAL COLLABORATION

1. Dr. Dick vanSoolingen, Netherlands, National Institute of Public Health and the Environment.
2. Dr. Philip Supply, France, Institute of Pasteur de lille.
3. Dr. Christophe Sola, and Nalin Rostagi from Guadeloupe, Institut of Pasteur de Guadeloupe.
4. Dr. Timothy McHugh, UK, Department of Medical Microbiology, Royal Free University College Medical School, London.
5. Utrecht University- Netherlands

THE

Biomedical Physics Department

The Biomedical Physics Department

Chairman
Belal Moftah, Ph.D., FCCPM

Deputy Chairman
Ghazi Alsbeih, MD, PhD

Administrative Support Staff
Banguilan, Irene, BSc (RC Grant Employee)
Co, Marilou, BSc (RC Grant Employee)
San Pedro, Mildred, BSc (RC Grant Employee)
Veridiano, Josephine, BSc

The Biomedical Physics Department concluded the year 2010 with commendable efforts of its staff members in the areas of service, consultation, research, continuing education and income producing activities.

Our physics support staff continued to implement advancement of clinical radiation physics services for cancer patients undergoing radiotherapy treatments with the latest technologies; conduct quality assurance monitoring of diagnostic radiology equipment; provide expertise in radiation protection and calibration of radiation-measuring instruments, and maintain the thermoluminescent dosimetry radiation dose monitoring system.

We have gained accreditation of our radiation physics procedures, machine output and the American RTOG protocols by the Radiological Physics Center of M.D. Anderson Cancer Center.

Our research activities have resulted in peer-reviewed publications that received recognition and awards. There have been a number of presentations and papers submitted, and in preparation from approved research projects in Biomedical Physics. We are committed to enhance our ability to conduct state-of-the-art research in clinical Biomedical Physics and continue to collaborate with counterparts at the forefront of current research.

Our continuing education program is focused on supporting relevant training and educational activities as well as organizing training courses, workshops and conferences. This is in addition to pursuing of board certification by internationally recognized certifying bodies and graduate study abroad for our staff as well as implementation of a residency program in medical physics and medical dosimetry. A departmental teaching is coordinated for the internal development of our staff through a semi-weekly seminar wherein staff members are encouraged to give lectures that reflect state-of-the-art practices.

The Department had trained two fellows from the International Atomic Energy Agency, and fifteen graduate and undergraduate students from different universities in the Kingdom during this reporting year.

One Saudi staff received a scholarship grant to pursue a Ph.D. study abroad, and one of our medical physicists passed the well-known American Board of Radiology examination. Other staff members are pursuing and preparing for similar recognized board certifications to further attest competency and maintain the integrity of our services.

We successfully hosted the International Conference in Radiation Medicine (ICRM) from 01 to 04 March 2010 (participated by more than 35 world-renowned speakers); the IAEA Course TRS457: Joint KFSH&RC/IAEA Advanced School on Dosimetry in Diagnostic Radiology and its Clinical Implementation, from 28 Feb to 04 March 2010; the 5th Saudi Conference in Medical Physics, from 19 to 21 October 2010; and the Intensive Course and Workshop: The World of Medical Physics, from 07 to 09 December 2010.

Our income producing activities remained active through consultation, personnel radiation monitoring and equipment calibration services, and gamma sterilizations on a fee for service basis, for different endpoints within and outside the hospital. There has been an increase in number of clients for the services that we provide.

The future of the department is largely dependent on the recruitment and retention of qualified staff needed to contribute to relevant programs that are in line with the core mission of KFSH&RC of improving the quality of patient care to the highest standard. There is an urgency to create new positions to cope with the increasing demand for services provided by the different sections of the Biomedical Physics Department particularly for our physics support responsibilities. The support of the Hospital and Research Centre administrations is critically needed to resolve the staffing shortage in the Department.

The activities of the four sections and four core facilities of the Department for 2010 are shown in separate reports.

RESEARCH PROJECTS

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

- KACST Grant Project #10-MED989-20: Functional Imaging of Infants and Toddlers with Autism. Principal Investigator: Rami Niazy, Ph.D.
- KACST Grant Project #09-MED 749-20: Developing Biological Dosimeters for the Assessment of Radiation Overexposure in Nuclear Accidents. Principal Investigator: Ghazi Alsbeih, M.D., PhD
- KACST Grant Project #10-BIO960-20: Development of Novel 30 Gel Dosimetry System for Radiation Oncology Treatment Verification. Principal Investigator: Belal Moftah, Ph.D., FCCPM

Three other KACST projects have been submitted for approval. Progress of the approved projects is reported separately by concerned sections.

FUTURE RESEARCH DIRECTION

The Department empowers its staff to have a protected time for research that is of relevance to improving the quality of patient care. Our future research direction is toward clinical research in Biomedical Physics in areas at the forefront of medical science today

PUBLICATIONS

A number of papers were published by the Department during 2010, some of which gained awards and recognition. Details of the publications and awards are shown in the sectional reports.

Published peer-reviewed papers are as follows:

- Alsbeih G, Al-Harbi N, Al-Hadyan K, El-Sebaie M, Al-Rajhi N. Association between normal tissue complications after radiotherapy and polymorphic variations in TGFB1 and XRCC1 genes. Radiation Research. Apr;173(4):505-11, 2010.

- G. Alsbeih and K. Al-Hadyan. Radiation therapy: How does it start and where does it end? Al Takhassussi magazine. No. 18: pp. 4-9, April 2010. Article in Arabic:

الاشعاعي: كيف يبدأ؟ واين ينتهي؟ مجلة التخصصي، السنة الخامسة، العدد (18)، ص9-4، ربيع الآخر 1431ه، ابريل 2010م.

- Al-Mohammed HI, Mahyoub FH, Moftah BA: Comparative study on skin dose measurement using MOSFET and TLD for pediatric patients with acute lymphatic leukemia. Med Sci Monit; 2010; 16(7):CR325-9.
- H. I. Al-Mohammed. Investigation of breathing maneuvers using free breathing and video biofeedback techniques during radiation therapy treatment for non small cell lung cancer patients. J Canc Rese Exp Onco.2010; 2(5): 60-71.
- Omar Chibani, Belal Moftah, C-M. Charlie Ma, On Monte Carlo Modeling of Megavoltage Photon Beams: A Revisited Study on the Sensitivity of Beam Parameters, Medical Physics 38, 188-201.

Biomedical Physics Research (Radiation Biology Lab)

Head

Ghazi Alsbeih, Ph.D.

Members

Najla Al-Harbi, BSc.
Muneera Al-Buhairi, B.Sc.
Khaled Al-Hadyan, B.Sc.
Sarah Al-Qahtani, B.Sc. (Grant)
L. Aubrey Venturina, B.Sc. (Grant)

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

RESEARCH PROGRESS

Project title

Identifying human papillomavirus infection, genotype, and p53 codon 72 polymorphism in Saudi cervix carcinoma patients treated with chemo-radiation therapy (ORA# 2060 027)

Investigators: Ghazi Alsbeih, Khaled Balaraj, Mostafa El-Haddad

Project description

Carcinoma of the uterine cervix is one of the most common neoplasias among women worldwide. Infection with human papillomaviruses (HPV) is the major etiologic cause, however, only a small number of women infected with high risk HPV develop cervical tumors, suggesting that other environmental and/or genetic factors contribute to cervical carcinogenesis. It has been suggested that Muslim women have lower incidences of cervical cancer and/or HPV infection raising the question of important environmental, cultural and genetic differences with western countries. Cervical cancer ranks number 8 in Saudi Arabian women forming 3.4% of newly diagnosed cancer cases; however, it is frequently diagnosed at advanced stages requiring chemo-radiation therapy. Since related studies are globally lacking in our local cancer population, this project proposes to investigate the association between HPV infection, HPV genotype, the patient's genetic predisposition in the tumor suppressor gene p53 codon 72 polymorphism and cervical cancer. These factors will also be evaluated for their prognostic significance for clinical chemo-radiation response. One hundred women with locally advanced cervical cancer treated with curative radiotherapy will be selected and DNA from paraffin embedded tumor tissues will be analyzed for HPV infection, HPV genotype, and p53 Arg72Pro polymorphism. Genetic p53 polymorphism will also be evaluated in 100 age-matched women with no history of cancer. Results should allow better understanding of the specificity, if any, of cervical cancer in our community and paves the way for the implementation of screening and prevention programs to reduce the high mortality related to delayed diagnosis.

Progress

100 cervical cancer samples were collected and HPV is being detected and genotyped. Results will be reported as soon as analysis is completed.

Project title

Study comparing radiosensitivity, DNA repair, misrepair and alterations in protein expression between fibroblasts derived from patients having different normal tissue reactions to radiotherapy: potential for a predictive assay (RAC# 2000 031).

Investigators: G. Alsbeih, PhD, N. Al-Rajhi, MD, A. Alaam MD, M. Al-Sebaie MD, Najla Al-Harbi, BSc, Muneera Al-Buhairi BSc

Project description and progress

Genetic predictive biomarkers of radiosensitivity are sought to individualize radiation treatment of cancer patients. In this case-control study, we tested the association between *TGFβ1* T10C Leu/Pro, *XRCC1* G399A Arg/Gln, and *XRCC3* C241T Thr/Met single-nucleotide polymorphisms (SNPs) and late reaction to radiotherapy in 60 nasopharyngeal cancer patients (Figure 1). Subcutaneous and deep tissue fibrosis was scored using RTOG/EORTC grading system. Patients with moderate to severe fibrosis (radiosensitive cases, G2-3, $n = 30$) were matched and compared to those with little or no reactions (controls G0-1, $n = 30$). The three nonsynonymous SNPs were genotyped by direct DNA sequencing. Genotype and allelic frequency showed significant association for *TGFβ1* T10C and *XRCC1* G399A ($P \leq 0.05$) (Figure 2). In addition, there was a significant difference in the median number of risk alleles associated with increased radiosensitivity (*TGFβ1* T10 and *XRCC1* G399) between the radiosensitive and the control groups ($P = 0.006$) (Figure 3). This study corroborates the association between both *TGFβ1* T10C and *XRCC1* G399A and risk of late complications following radiotherapy in our local patients. It also lends support to the assumption that radiosensitivity depends on the combined effects of SNPs in several genes. However, possible dissimilarity between populations and probable segregation with other genetic variations warrant large multinational studies looking at panoply of polymorphisms.

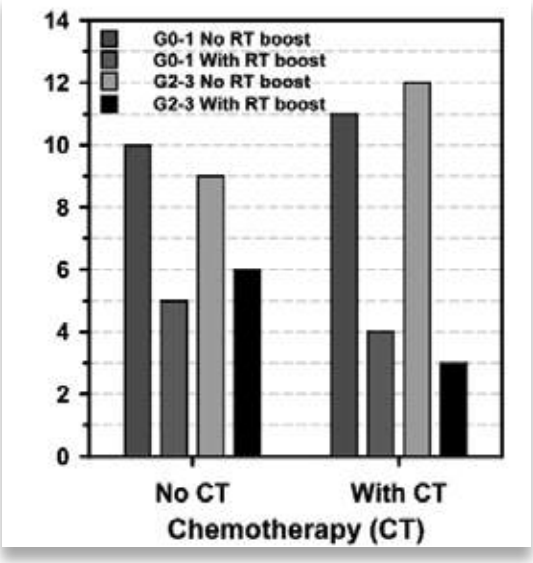


Figure 1. Distribution of the 60 nasopharyngeal carcinoma patients according to the chemotherapy and the radiotherapy boost received. The patients developed either minimal (control: G0-1) or substantial (radiosensitive: G2-3) fibrotic reactions following radiotherapy.

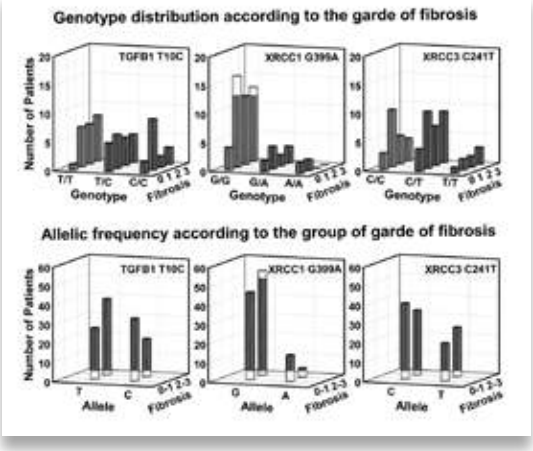


Figure 2. Genotype and allelic distribution of the three assessed polymorphisms in 60 nasopharyngeal cancer patients who developed different grade of radiation-induced fibrosis

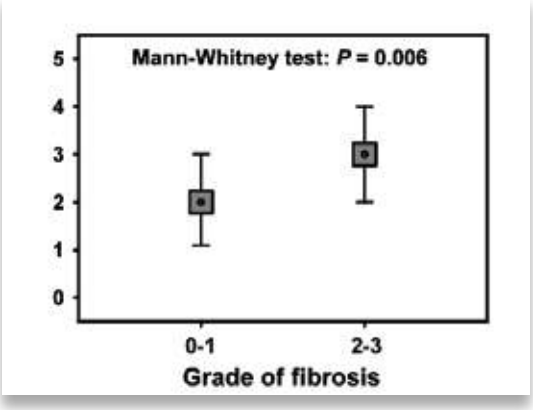


Figure 3. Analysis of the relationship between the number of risk alleles and the grade of fibrosis following radiotherapy. Patients were separated into two groups: control (G0-1 fibrosis) and radiosensitive (G2-3 fibrosis). The squares represent the median number of risk alleles. Bars above and below squares indicate the 90th and the 10th percentiles, respectively.

FUTURE RESEARCH DIRECTION

We are expanding our work on cervix carcinoma in Saudi Arabia and its relationship with HPV infection, genetic predisposition and biomarkers of response to chemo-radiation therapy. We have also started a new project to establish a national biodosimetry laboratory.

PUBLICATIONS

- Alsbeih G, Al-Harbi N, Al-Hadyan K, El-Sebaie M, Al-Rajhi N. Association between normal tissue complications after radiotherapy and polymorphic variations in TGFB1 and XRCC1 genes. Radiation Research. Apr;173(4):505-11, 2010.
- G. Alsbeih and K. Al-Hadyan. Radiation therapy: How does it start and where does it end? Al Takhassussi magazine. No. 18: pp. 4-9, April 2010. Article in Arabic:

الاشعاعي: كيف يبدأ؟ واين ينتهي؟ مجلة التخصصي، السنة الخامسة، العدد (18)، ص9-4، ربيع الآخر 1431ه، ابريل 2010م.

ABSTRACTS/CONGRESS PROCEEDINGS

- Ghazi Alsbeih, Najla Al-Harbi, Raef Ahmed, Asma Tulbah, Hani Salem, Ismail Albadawi, Osama Alomar, Murad Al-Aker, L. Aubrey Venturina, and Khaled Balaraj. Prevalence of HPV genotypes in cervical cancer in Saudi Arabia. 26th International Papillomavirus Conference & Workshop, Montreal, Canada, 03 - 08 July 2010.
- Al-Hadyan K, Al-Harbi N, Al-Qahtani S, Al-Buhairi M, Alsbeih G. Involvement of Single Nucleotide Polymorphisms in Predisposition to Cancer of Head and Neck in Saudi Patients. The 3rd Pan Arab Human Genetics Conference (PAHGC 2010). Dubai, United Arab Emirates, 13-14 March 2010.
- Alsbeih, Ghazi; Al-Harbi, Najla; Al–Qahtani, Sara; Venturina, L. Aubrey; Awad, Raef; Balaraj, Khaled, The association between p53 codon 72 polymorphism, human papillomavirus infection and cervical cancer in saudi Arabia. International Conference on Radiation Medicine: Clinical Applications and Innovative Approaches. FSH&RC, Riyadh, Saudi Arabia. 01 - 04 March 2010.
- Venturina, L. Aubrey, Al-Qahtani, Sara, Alsbeih, Ghazi. Role of research coordinator in organizing clinical projects involving patients undergoing multi-modalities cancer treatment. FSH&RC, Riyadh, Saudi Arabia. 01 - 04 March 2010.
- Al-Hadyan, Khaled; Al-Harbi, Najla; Al-Buhairi, Muneera; Rajab, Mohamed; and Alsbeih, Ghazi. Radiosensitivity of a novel mre11 mutation responsible for the ataxia telangiectasia-like disorder in Saudi Arabia. FSH&RC, Riyadh, Saudi Arabia. 01 - 04 March 2010.
- Al-Buhairi, Muneera; Moftah, Belal; Alsbeih, Ghazi. Uses of radiobiological models to predict normal tissues complications following radiotherapy. FSH&RC, Riyadh, Kingdom of Saudi Arabia. 01 - 04 March 2010.
- Al-Harbi, Najla; Al-Buhairi, Muneera; Al-Hadyan, Khaled; El-Sebaie, Medhat; Al-Rajhi, Nasser; Alsbeih, Ghazi. Relationship between genetic polymorphic variations in cell cycle and DNA repair genes and complications to radiotherapy in Saudi head and neck cancer patients. FSH&RC, Riyadh, Saudi Arabia. 01 - 04 March 2010.

AWARDS AND HONORS

- Recipient of the Hamdan Award for Original Research Paper published in the Journal of Medical Sciences for the year 2009-2010. The award was presented on 13th of December 2010 by Sheikh Hamdan Bin Rashid Al Maktoum, Deputy Ruler of Dubai, United Arab Emirates.

Clinical Dosimetry and Treatment Planning Unit

Head

Belal Moftah, PhD

Members

Ghada Al Dosary, BSc (RC Grant Employee)
Badraldeen Al Tazi, BSc (RC Grant Employee)
Manal Awidah, BSc (RC Grant Employee)
Ghadeer Nazer, BSc
Wedyan Safar, BSc, CMD
Hind Al-Selham, MSc
Ericka Venturina, BSc (RC Grant Employee)
Paula Yates, RT(T), CMD

2010 was an active year within the Dosimetry Unit as it was for the Radiation Physics Section as a whole. We received advanced training for planning of Cyberknife, Tomotherapy and RapidArc modalities and, in turn, trained others in a series of Workshops held throughout the year. As a result of our advancement in knowledge of planning using the modalities mentioned above our patient numbers, for those modalities, more than doubled.

For 2011 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.

CORE SERVICE ACTIVITIES

ACTIVITIES	YEAR 2010
Monitor Unit (MU) Calculation/2-Dimensional Contour	407
Total Body Irradiation (TBI) Calculation	70
3-Dimensional CT Treatment Planning	1115
Stereotactic Radiosurgery/Radiotherapy (BrainLab)	0
Electron Cut-out Measurement	110
Intensity Modulated Radiation Therapy (IMRT)	247
RapidArc	65
Tomotherapy	119
Cyberknife	122
TLD Dosimetry	60
Total Skin Electron Treatment (TSET)	2
High Dose-Rate (HDR) Brachytherapy	21
Low Dose-Rate (LDR) Brachytherapy	17
Clinical Consultation	48
Free-Hand Set-Up (FHSU)	2
TOTAL PROCEDURES	**2405**
PATIENTS	**1319**
MANHOURS	**10400***

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

TRAINING AND EDUCATION ACTIVITIES

The main event for our staff, as participants and instructors, was the International Conference of Radiation Medicine (ICRM) held in March 2010 at KFSH&RC.

Hind Al-Selham, MSc attended the Varian IMRT and RapidArc Course in Switzerland in November and then, as a follow-up to that course, the Varian IMRT and RapidArc School in France in December 2010. She will move out of the Dosimetry Unit to enroll in the KFSH&RC/ARASIA Residency Program for Medical Physicists in Radiation Oncology in early 2011.

Manal Awidh, BSc, Ghadeer Nazer, BSc and Ericka Venturina, BSc all plan to sit for the American Certified Medical Dosimetry Board examination in September 2011.

Badr Al Tazi, BSc joined the Unit in March 2010 and will resign in early 2011 to pursue a Masters degree in Medical Physics in the United States of America.

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.

The main educational advancement in 2011 will be the commencement of the KFSH&RC/ARASIA Residency Program for Medical Physicists in Radiation Oncology. At any given time during the program there will be up to two residents rostered into the Dosimetry Unit for training. In addition there is a proposal to have a Dosimetry Residency/Training Program commencing in 2011 as well.

STAFFING

Due to our continuing staff shortage, made worse by senior staff resignations at the end of 2009 and non-recruitment into these vacant positions through-out 2010, we continue to rely on our colleagues from the Radiation Physics Section as well as additional physics graduate Grant Employees to assist us in our workload.

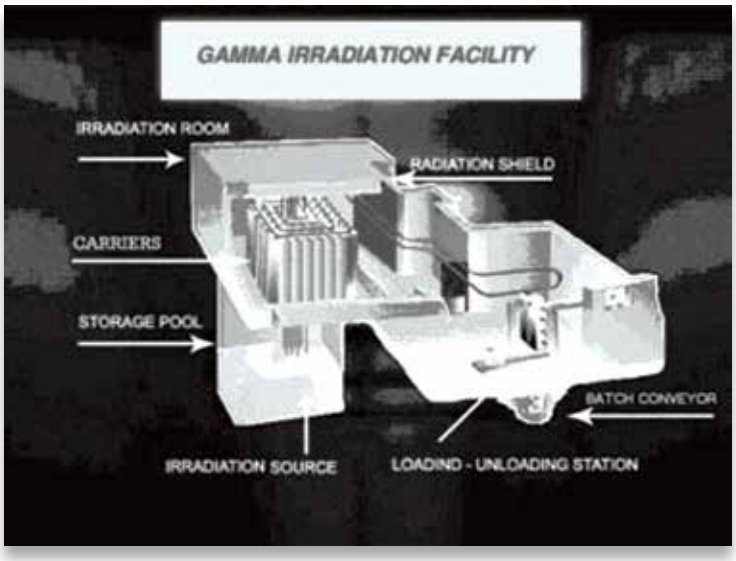
The Dosimetry Unit hopes to recruit new senior staff in 2011 to enable our participation in research activities and production of scientific papers based around our knowledge of advanced radiation treatment modalities.

Gamma Irradiation Facility

Head
Akram Al-Moussa, BSc

Members
Saad Bin-Jamaan, BSc
Edilberto Delos Reyes

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.



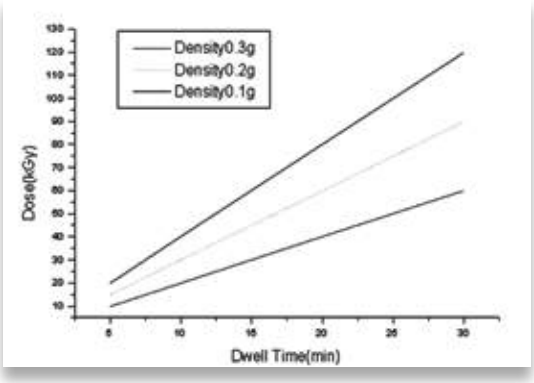
CORE SERVICE ACTIVITIES

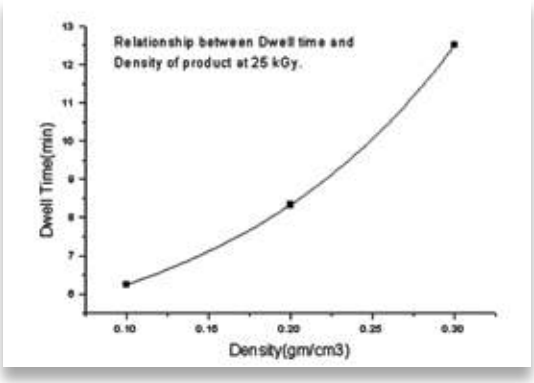
The activities of the Gamma Irradiation Facility in 2010 are as follows:

1. Continued to provide sterilization for hospital needs (Cyclotron kits, Biomedical Research and supplies of ART laboratory.
2. Provided gamma irradiation services for Master Degree students from different scientific institutes, with doing the necessary dosimetry for there samples.)
3. New research project with KACST on the 3 D-Gel dosimetry for cancer patients' therapy is guaranteed for the coming two years. A lot of scientific and clinical work are expected though this project.
4. Bone bank of the KFSH&RC is opened and services of sterilization of bone grafts started. Special dosimetry procedures are 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.





Health Physics Section

Head

Fareed Mahyoub, MSc, MIPEM

Members

Ibrahim Al-Gain, BSc
Rami Al-Harbi, BSc (RC Grant – until October 2010)
Noura Al-Mulhem, BSc (RC Grant)
Amal Al-Mutairi, BSc (RC Grant – until January 2010)
Arwa Helmi, BSc (RC Grant)
Celestino S. Lagarde, BSc

The Health Physics Section of the Biomedical Physics Department has continued to provide services in line with its mission of limiting the risks of exposures to patients, staff and members of the public. Our institution, through our Health Physics program, is recognized by the International Atomic Energy Agency (IAEA) as a center for training in radiation protection and measurement. The section's 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 and other institutions within the Kingdom are also provided by the section on a fee for service basis.

ACTIVITIES AND ACCOMPLISHMENTS

There is an increase in the Health Physics work activities during 2010. We have a number of new clients for our TLD radiation monitoring services.

Our staff members have continued to provide Health Physics services for patients treated with radioactive iodine 131 in F-1 and Cesium-137 in A-3 at KFSH&RC as well as for Eye Plaque procedures at King Khaled Eye Specialist Hospital.

Our section was actively involved in the orientation and training of students from universities within the Kingdom.

The section is represented at meetings of different Hospital committees, and actively providing consultation services on matters related to monitoring of radiation doses and exposures for patients, staff, members of the public and the environment.

One staff member obtained Corporate Membership of the Institute of Physics and Engineering in Medicine (MIPEM), UK, demonstrating high standard scientific and professional attainment.

The following table briefly summarizes the accomplishments of the Health Physics Section for the year 2010 in providing services to the KFSH&RC, to other institutions in the Kingdom of Saudi Arabia and neighboring countries in the Gulf region:

Task Descriptions	Quantity
Radiation workers monitored for occupational doses	3600
Patients surveyed for radiation level	238
Patients rooms surveyed for radiation level	238
Patients rooms decontaminated	238
Leak tests conducted for sealed sources and radiation producing equipment	114
TLD badges irradiated for quality control of TLD readers of outside facilities	111
Consultative advice provided	14
Training courses & educational lectures provided	15

Imaging Physics Section

Head

M. Gary Sayed, Ph.D., FACNM

Members

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

Most of the activities in the imaging physics section are concentrated in providing clinical medical physics services to the departments of Medical Imaging Services, OR, Dentistry, Cath Lab and Radiotherapy of the KFSH&RC (Riyadh); the department of Radiology of the King Fahad National Children's Cancer Centre & Research (KFNCCC&R), Royal Palace satellite clinics and mobile vans. Imaging modalities served by our staff 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.

RESEARCH PROJECTS

Project title

Lesion Quantification in Whole Body Images of Positron Emission Tomography (PET).

Investigator: O. Demirkaya

Project description

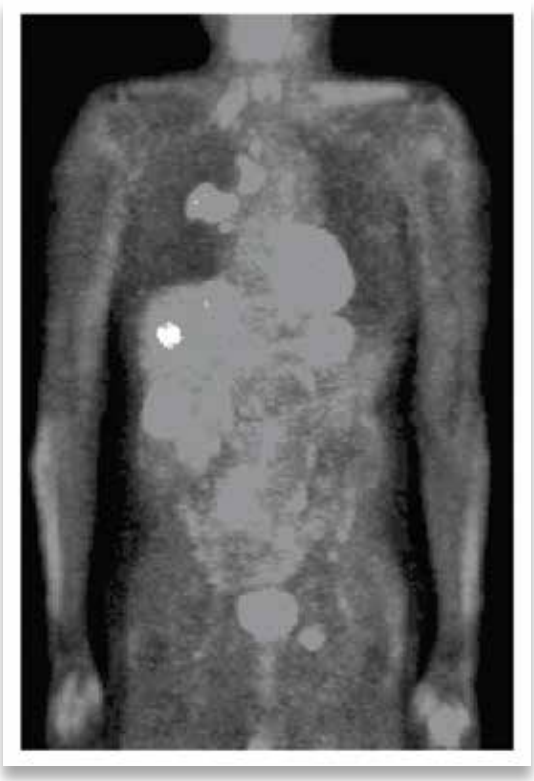
In PET, identification of lesion boundaries in general is not a trivial problem as whole-body images exhibit inhomogeneity. Manual methods discourage physicians from taking advantage of the inherently quantitative data and help them opt for qualitative means in their diagnosis and assessment of the patient 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

Two main research activities are underway in the Section. The first project is directed toward PET/CT applications in medicine where imaging applications are being developed to assist radiologists in improving their clinical protocols to improve diagnostic detection of malignant disease via the use of image analysis and quantification techniques. This research will also assist the institution in optimizing modality utilization (PET/CT verses just CT or MRI) thus minimizing the time of diagnosis and reducing radiation exposure to patients. The other main project is slated to be launched in the summer of 2011 and involves the in-vitro dosimetric assessment of targeted radionuclidic therapy applications of new beta-radiation emitters such as Lu-177.



Molecular and Functional Imaging

Head
M. Gary Sayed, Ph.D., FACNM

Member
Rami Niazy, Ph.D.

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

Radiation Physics Section

Head

Belal Moftah, Ph.D., FCCPM

Members

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

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 Physics team played a vital role in the effective and safe clinical utilization of the three major radiotherapy treatment modalities TomoTherapy, CyberKnife, and RapidArc. One major undertaking of the Section is the launching of the formal medical physics residency training program. The Clinical Dosimetry and Treatment Planning Unit, 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 of the major radiotherapy treatment modalities at KFSH&RC.

RESEARCH PROJECTS

Project title

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

Principal Investigator: Belal Moftah

Project description

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

Progress

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

Project title

Development of Novel 3D Gel Dosimetry System for Radiation Oncology Treatment Verification.

Principal Investigator: Belal Moftah

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 approved SR 2.0 Million).

Project title

Developing Biological Dosimeters for the Assessment of Radiation Overexposure in Nuclear Accidents.

Co-Principal Investigator: Belal Moftah

Project description

KACST Advanced and Strategic Technologies program of the National Comprehensive Plan for Science and Technology. (Project # 08-MED749-20, 24 months, approved for funding, SR 2,000,000).

FUTURE CLINICAL RESEARCH DIRECTION

Project title

Intra-Operative Proton Radiotherapy (IOpRT)

Principal Investigator: Belal Moftah

Project description

A grant proposal submitted to KACST's Advanced and Strategic Technologies program of the National Comprehensive Plan for Science and Technology. (Project: 11-BIO1428-20, 24 months, requested budget SR 2,000,000)

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

PUBLICATIONS IN REFERRED JOURNALS

- Omar Chibani, Belal Moftah, C-M. Charlie Ma, On Monte Carlo Modeling of Megavoltage Photon Beams: A Revisited Study on the Sensitivity of Beam Parameters, Medical Physics 38, 188-201.
- Al-Mohammed HI, Mahyoub FH, Moftah BA: Comparative study on skin dose measurement using MOSFET and TLD for pediatric patients with acute lymphatic leukemia. Med Sci Monit; 2010; 16(7):CR325-9.
- H. I. Al-Mohammed. Investigation of breathing maneuvers using free breathing and video biofeedback techniques during radiation therapy treatment for non small cell lung cancer patients. J Canc Rese Exp Onco.2010; 2(5): 60-71.

PRESENTATIONS AT CONFERENCES AND MEETINGS

(Presenting author *)

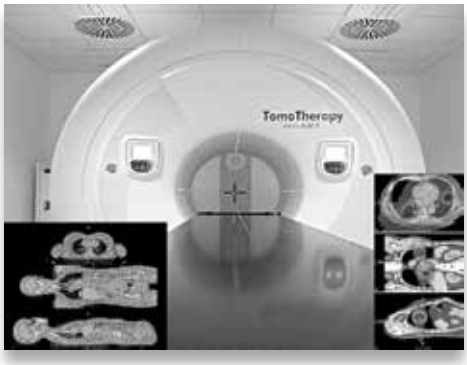
- O. Chibani*, B. Moftah and C. Ma; On Monte Carlo modeling of Megavoltage Photon Beams: A revisited Study on beam parameters sensitivity, 52nd Annual Meeting of the American Association of Physicists in Medicine (AAPM), Philadelphia, USA, July 18-23, 2010.
- Belal Moftah*, Comments on IAEA's Role in the Fight against Cancer in the Developing Countries, International Atomic Energy Agency (IAEA) Scientific Forum: Cancer in Developing Countries Facing the Challenge, September 21-22, 2010, Vienna, Austria. (Invited Speaker)
- Belal Moftah*, Medical Physics in Saudi Arabia, Intensive Course and Workshop: The World of Medical Physics, Riyadh, December 7, 2010. (Invited Speaker)
- Belal Moftah*, Advanced Radiotherapy Techniques, Intensive Course and Workshop: The World of Medical Physics, Riyadh, December 8, 2010. (Invited Speaker).

PUBLISHED ABSTRACTS

- M.A. Kafi and Belal Moftah, Poster Abstract # 3432, Evaluation of a Monte Carlo Based Commercial Electron Beam Treatment Planning System, 52nd Annual Scientific Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), October 31 – November 4, 2010, San Diego, CA.
- Omar Chibani, Belal Moftah, Charlie Ma, Abstract ID: 13001 Title: On Monte Carlo Modeling of Megavoltage Photon Beams: A Revisited Study on Beam Parameters Sensitivity, Medical Physics 37 (2010) 3278.

THREE MAJOR RADIOTHERAPY TREATMENT MODALITIES AT KFSH&RC

CYBERKNIFE



TOMOTHERAPY

RAPID ARC

Radiation Safety Office

Head
Fareed H. Mahyoub, MSc, MIPEM

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

The Radiation Safety Office (RSO) is responsible for implementation of the radiation safety program of the King Faisal Specialist Hospital & Research Centre. The RSO is committed to attain the goal of optimizing the use of ionizing radiation for quality patient care. Consistent with the international recommendations, the hospital radiation safety infrastructures are in place and are continuously reviewed by the RSO to guarantee that the benefits derived by the patients from such radiation applications are maximizing the risks to patients, staff, members of the public and environment. The RSO is charged with the responsibility to provide a radiation safe working environment at KFSH&RC.

The RSO is the only office at KFSH&RC that coordinates and liaises with King Abdulaziz City for Science and Technology (KACST) and other national regulatory agencies on the purchase, use, transport and disposal of radioactive materials and radiation emitting equipment. To maintain the high standards of radiation safety it reviews and recommends to the Radiation Safety Committee (RSC) approval of authorizations for use of radioactive materials; implements the KFSH&RC policies on radioactive waste management and monitors radiation safety practices and radiation levels in work areas. The RSO has competent and qualified staff members who undertake investigation and provide technical consultation and services in the event of radiation incidents and emergencies. It approves radiation shielding designs and participants in the acceptance tests of radiation emitting equipment to ensure patient and staff safety. It plays a vital role in the decommissioning of radiation emitting devices. The RSO together with the Health Physics Section of the Biomedical Physics Department have a well established education and training programs and good training facilities for KFSH&RC personnel, International Atomic Energy Agency (IAEA) fellows and for trainees from West Asia region.

SIGNIFICANT ACHIEVEMENTS

- Obtained KACST approval to renew the license to import radioactive materials.
- Obtained KACST approval for amendment of Nuclear Medicine License.
- Obtained KACST approval to renew the license of scientific research for another two years.

CONTINUING EDUCATION/TRAINING

The RSO conducted two (2) in-house lectures and provided a one-week on-the-job training on radiation safety to two (2) university students.

COLLABORATION

National collaboration is made with KACST, Ministry of Health and Ministry of Interior. International collaboration with IAEA and international societies is maintained.

PROJECT IN PROGRESS

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

DATA

For the year 2010, the RSO applied for amendment of the KFSH&RC license from KACST for the radiation facilities of Nuclear Medicine and the Radio-Isotopes Production and both applications have been successfully approved. It has renewed the KACST license to import radioactive materials and has submitted the application for the amendment of a license for the Radiation Therapy facility. It has also renewed the license of scientific research for another two years. In radiation measurements, there were 357 incoming radioactive sources and 2028 out-going packages of radioactive materials surveyed. In the principle of "As Low as Reasonably Achievable" (ALARA), 103 investigations were carried out on staff whose occupational doses exceeded the ALARA levels; 24 thyroid bioassays were performed. Five work areas and 2 equipments were surveyed for radiation and contamination levels. A total of 45 radioactive sealed sources were checked for inventory and 11 leak tests were undertaken. The RSO responded to 2 radiation incidents and provided 4 technical consultations. In the area of radioactive waste management, the generated radioactive wastes were managed by the decay-in storage method where 75 drums were surveyed and stored in Radioactive Waste Storage. In education and training the RSO conducted 2 in-house lectures and provided a one-week on-the-job training on radiation safety to 2 university students and 2 new radiation workers. The RSO has maintained its collaboration within the Hospital and with national and international bodies. Four RSC meetings were coordinated and the Office continued to have collaboration with other Hospital committees.

Secondary Standard Dosimetry Laboratory

Head
M. Gary Sayed, Ph.D., FACNM

Members
Nabil Iqeilan, MSc
Heba Al-Humaidan, BSc

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

ACTIVITIES

For the year 2010, the SSDL provided calibration services to 5 departments of KFSH&RC, 12 government agencies and hospitals, 7 private hospitals, 49 private companies [Fig 1]. A total of 1295 radiation-measuring instruments were calibrated, inter-compared and acceptance tested. These instruments include 1015 survey meters, 234 pocket dosimeters [Fig. 2]. To ensure accuracy in its calibration, the SSDL participated in the IAEA and WHO annual postal dose audit for radiotherapy energy level of calibration where it obtained a very satisfactory result.

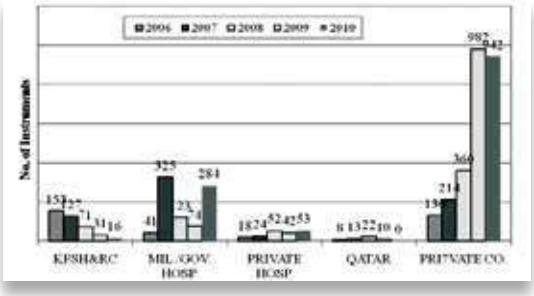


Figure 1. Graph showing the number of external facilities served and the number of instruments calibrated for each group by the SSDL.

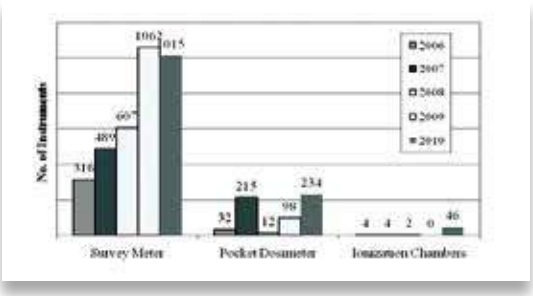


Figure 2. Graph showing the type and number of instruments calibrated.

THE

BioMolecular Research Program

The BioMolecular Research Program

Director

Khalid S. Abu Khabar, Ph.D.

Members

Edward Hitti, Ph.D., Associate Scientist
Anas Al-Halees, Ph.D., Post Doctoral Fellow
Fahad Al-Zoghaibi, Ph.D., Post Doctoral Fellow
Walid Moghrabi, M.Sc., Senior Specialist
Latifa Al-Haj, BSc., Research Associate
Maha Al-Ghamdi, M.Sc., Research Assistant
Wijdan, Al-Ahmadi, B.Sc., Research Assistant
Maher Al-Saif, B.Sc., Research Technician
Lina Omar, Research Technician
Suhad Al-Yahya, Research Technician

Functional Sections

Bioinformatics
Interferons and Cytokines (Mechanisms of Disease)
Molecular Biotechnology
Molecular Therapeutics (future)

The ultimate goal of the research program is to focus on the 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.

OVERVIEW OF SELECTED 2010 ACHIEVEMENTS

- Two PCT patent applications were filed in 2010 entitled.
- Three Funded grants from KACST-National Plan for Science & Technology Program and King Saud University (Center for Excellence in Biotechnology)
- Research demonstrated that the tristetraprolin is deficient in highly invasive breast cancer cells and restoration of this gene leads to a significant reduction of the invasiveness of the cells. Furthermore, the study showed that TTP suppressed several gene products that have prominent roles in breast cancer invasion and metastasis. Published in Oncogene, 2010.
- A new approach was described and published in RNA journal (see publication list below) comprising methods that can specifically detect post-transcriptional gene regulation- i.e., at events that follow the transcription. The method can facilitate large scale studies such as drug target and drug screening without involvement of nucleic acids extraction. As a matter of fact, an international PCT patent application was filed in 2009 with national phases entered in U.S., EU, and Canada at 2010/2011.
- Invited review article with a cover page in Cellular Molecular Life Sciences journal (see publications list below).
- Al-Ghad Award for Biomedical Innovation-Sponsored by Crown Prince, 2010.

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

- Anas Al-Halees, Edward Hitti, Maher Al-Saif, Lina Mahmoud, Irina Vlasova, Dan Beisang, Suhad Al-Yahya, Paul Bohjanen, Khalid S. A. Khabar*. 2010. A Global Assessment of the GU-Rich Regulatory Content of the Human Transcriptome. *RNA Biology*. In press.
- Edward Hitti and Khalid S. A. Khabar. 2010 Sequence variations affecting AU-rich element function and disease. *Frontiers in Biosciences*. Invited Review.
- Edward Hitti, Suhad Al-Yahya, Maher Al-Saif, Peer Mohideen1 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*. 16(6):1245-55.
- Nora Al-Suhaibani, John E. Hesketh, Perry J. Blackshear3, and Khalid S. A. Khabar* 2010. The RNA Binding Zinc Finger Protein Tristetraprolin Regulates AU-Rich mRNAs Involved in Breast Cancer-Related Processes. *Oncogene*. May 24.
- Khabar, K.S. Post-transcriptional control during chronic inflammation and cancer: a focus on AU-rich elements. Cell Mol Life Sci. 2010 May 22. Invited Review.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. 2009. Temporary regulated traffic of HuR and its associated ARE-containing mRNAs from the chromatoid body to polysomes during mouse spermatogenesis. *PLoS ONE*. 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. 2009. *Nucleic Acids Research*. 16;28(15):1782-91.
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- 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.

INVITED TALKS AND ORAL PRESENTATIONS

- **Oral Presentation.** Plenary Session. Invasion of breast cancer as a highly deregulated RNA Stability phenomenon. Breast Cancer Frontiers. Riyadh, 2010.
- **Oral Presentaion.** Plenary Session. Biological and Pathological Ramification of Aberrations In AU-rich Elements-Mediated Pathways. 4th RNA Turnover Meeting. October. Montreal, Canada, 2010.
- **Invited Talk.** Plenary Session. The role of RNase L in health and disease: RNase L is a mediator of responses in innate immunity and cellular growth. 8th RNases Meeting. Naples, Italy, 2010.
- **Invited Speaker.** mRNA turnover in immune cells. Invited Talk. African City Biotechnology Conference. October, Khartoum.
- **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.
- **Molecular response to therapeutic interferons.** Sensitivity and resistance mechanisms. 1st International Conference on Drug Design & Discovery. Dubai. February 4-7. 2008

PATENTS/PATENT APPLICATIONS:

1. International Patent Application. JANUARY, 2010. PCT/EP. "A METHOD FOR INCREASING PROTEIN EXPRESSION IN EUKARYOTIC CELLS".
2. International Patent Application. August 2010. "FLUORESCENT PROTEINS WITH INCREASED ACTIVITY IN CELLS". International Patent Application. 2009. "INCREASING PROTEIN EXPRESSION IN EUKARYOTIC CELLS BY INCREASING RNA STABILITY".
3. European Union Granted Patent.
4. International Patent Application 2009. "METHODS FOR PRODUCING INDUCIBLE AND/OR REPRESSIBLE EXPRESSION ACTIVE LINEAR RNA INTERFERENCE CASSETTES AND INDUCIBLE AND/OR REPRESSIBLE EXPRESSION ACTIVE LINEAR GENE CASSETTES AND THEIR USES".
5. Granted Patent (EU). METHOD OF GENERATING TRANSLATIONALLY ACTIVE LINEAR DNA MOLECULES AND USE THEREOF IN ARRAY FORMATS. 2009.
6. International Patent Application. November 17, 2008. PCT/EP2008/009712. "EXPRESSION VECTORS BASED ON MODIFIED RIBOSOMAL PROTEIN PROMOTERS AND USES THEREOF IN POST-TRANSCRIPTIONAL ASSESSMENT".
7. International Patent Application. June 27, 2008. PCT/EP2008/005278."CLONING-FREE METHOD OF GENERATING TRANSCRIPTIONALLY AND POST-TRANSCRIPTIONALLY CONTROLLABLE EXPRESSION ACTIVE LINEAR REPORTER CONSTRUCTS.

THE DEPARTMENT OF

Biostatistics, Epidemiology and Scientific Computing

The Department of Biostatistics, Epidemiology and Scientific Computing

Chairman

Mohamed Shoukri, PhD

Administrative Staff

Alia Gabr
Cielo Dupaya Mendiola
Ismail El Sayed Mohamed
Abel Pangilinan

Overview of Research Activities

BIOSTATISTICS EPIDEMIOLOGIC RESEARCH AND INFORMATICS

The Biostatistics, Epidemiology, and Scientific Computing Department (BESC), located in the Research Center is an institutional resource for The King Faisal Specialist Hospital and Research Center. The BESC is developing the full range of biostatistics, and epidemiologic capabilities within the KFSHRC. These capabilities are anticipated to assist in the development of cost-effective health care policies and programs for the improvement of the health of the patients of this great institution.

The BESC staffs spare no effort in making their mission an integrated part of the Research Center and the Hospital mission. We try our best to promote the strategic growth of the biostatistics and epidemiologic capacity through: (1) the generation, synthesis, and dissemination of high-quality biostatistics and epidemiologic information on health conditions of high priority; and (2) education and training opportunities designed to develop and enhance variety of technical expertise.

RESEARCH

Our research portfolio is comprised of support of intramural and extramural projects that contribute to the current understanding of the natural history/clinical course of diseases of high priority to the Kingdom. These projects contribute to the current epidemiologic understanding of the following priority conditions: congenital heart diseases, mental health, diabetes mellitus, epilepsy, and other severe chronic diseases.

We provide technical consultation and rapid response to requests from clinical and research departments across the hospital. Technical consultation is also provided to investigators who require assistance in planning or conducting medical and basic research, including proposal or project review and technical advice or participation as consultants or investigators on proposed or funded research. In addition, through our registry core facility and technical database units, we provide ongoing monitoring of disease patterns or health profiles among our patients to identify new priorities for health conditions and, hence, emerging areas for policy development, including the targeting of research activities.

TRAINING AND EDUCATION

We provide education/training in biostatistics, and epidemiologic research methods. This involves either provision, or coordination of access to biostatistics courses (i.e., short courses, seminars and workshops); research-based training opportunities (within and outside the projects comprising the research portfolio). We coordinate our educational activities through the Training and Education Office of the Research Center and the Training and Development of the Hospital.

Our computing services technical staffs are key resources that are essential to the high-quality performance of all core functions in the Research Center.

To strengthen our functional strategy, and add to the value chain in our department, and with the support and approval of the Research Center Administration, a new group (Evidence-based and Decision Support Unit) has been established. This is a cross-functional group with a highly leveraged entity, whose chief aim is to link with a broad array of relevant Departments and the Executive branch of the hospital.

The BESC continues to grow and diversify its activities in order to serve our colleagues and help our organization achieve its goals.

Biostatistics Research Unit

Head

Mohamed Shoukri, PhD

Members

Dilek Colak, PhD
Abdelmuniem Eldali, MSc
Salah I. Al Gain, MSc
Wilhelmina Ventura
Samia Al-Hashem

Project title

Likelihood inference on the relative risk in split-cluster designs, RAC# 2090030.
Project Investigators: M.M.Shoukri and D. Colak

Project description

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

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

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

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

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

Progress

A paper has been submitted to the Clinical Trials Journal and will appear in 2011.

Project title

Establishing Equivalence of Two Treatments using Neyman's C (α) Test, RAC # 2050002.

Investigators: M.M.Shoukri and D. Colak

Project description

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

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

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

Progress

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

Project title

Hunting for one of the Autism genes that might linked to osteopetrosis with renal tubular acidosis. RAC # 2030-046.

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

Project description

This proposal is to investigate patients with osteopetrosis and renal tubular acidosis with autism. A region where carbonic anhydrase 2, the deficient protein in osteopetrosis and renal tubular acidosis is centered will be studied for (a) polymorphic markers using Affymetrix high density SNP chips B) carbonic anhydrase 2 gene mutations; 3) for possible inversion within the region or 4) for possible microdeletion in the region, 5) global gene expression profiling using Affymetrix's GeneChips. It is anticipated that a gene or genes linked to autism will be thus identified, differences in phenotype will be determined based on gene expression studies and these results should contribute to the research on autism-associated gene markers.

Progress

The whole-genome mRNA expression profile in lymphoblastoid cells from patients and age and sex matching controls were performed by using Affymetrix GeneChip Human

Genome U133 Plus 2.0. 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. Genotyping and mutation screening were also performed and found a novel mutation for OPRTA. Presented at international/local conferences, one manuscript is currently under review, and another manuscript is under preparation.

Project title

Molecular genetic studies in chromosome disorders, RAC #2040 042.

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

Project description

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

Progress

We have collected samples from patients (mainly children) based on our inclusion criteria. We performed high-resolution aCGH using Agilent high-density chips, linkage, CNV, and genome-wide gene expression studies using Affymetrix GeneChip SNP and gene expression assays. We performed the data analysis and obtained initial results. We are 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. A manuscript is published in Molecular Cytogenetics and another manuscript is under preparation.

Project title

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

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

Project Project description

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

Progress

We have performed gene expression profiling using Affymetrix's Human HG-U133 Plus 2.0 gene expression chips on whole blood RNA from patients and sex and age matching controls. We have identified significantly altered genes that are common among the autism spectrum diseases. Functional and pathway analysis have been performed. One manuscript is published in "Genomics", 2011, and another manuscript is under preparation.

Project title

Pathogenesis of Early Infantile Primary Lactic Acidosis, RAC Project # 2050-009.

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

Project description

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

Progress

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

Project title

Gene expression and immunohistological finding in patients with Papillion Lefevre Syndrome, RAC# 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

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

Project title

Proteomic analysis of human breast cancer stem cells/ progenitor cells, RAC # 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 have used stem cell markers to isolate cancer stem cells and subjected to proteome analysis by 2-DE. Global protein fingerprints were generated from sorted normal progenitor/stem cells adjacent to tumor as well as normal breast tissues from healthy individual. The results are presented at an International conference.

Project title

Identification of Environmental and Genetic Factors that Influence Breast cancer development and therapy in Saudi females, RAC# 2031091.

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

Project description

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

Progress

We analyzed the whole-genome mRNA expression profile from tumor and adjacent disease free tissues of 115 samples

using Affymetrix GeneChip Human Genome U133 Plus 2.0 Arrays. Both unsupervised and supervised analyses were performed. We have identified 77 signature genes specific to tumor in young age (≤ 45). 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. Breast cancer appearing in young women represents distinct biological characteristics with unique deregulated signaling pathways. We presented our results at local and international conferences. One manuscript is submitted for publication.

Project title

Positional Cloning of genes underlying genetics disorders with prominent neuro-developmental manifestations in several extended families, RAC# 2060 035.

Investigators: N Kaya, D Colak, and M Al-Sayeed

Project description

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

Progress

DNA samples have been collected from consanguineous familes. SNP-based genotyping, linkage analysis, homozygosity mapping and mutation analysis were performed. A novel mutation is found. A manuscript is published in Clinical Genetics, 2011. Another manuscript under preparation.

Project title

Genomics, Transcriptomics, and Proteomics Analysis of Ovarian Hyperstimulation Syndrome: A comprehensive molecular look to a complex syndrome. (Grant from KSU-KACST Joint Grants Support for Center of Excellence), RAC#2100 002.

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

Project description

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

Progress

This project has been recently approved by KSU-KACST Joint Grants Support for Center of Excellence, and RAC. Sample collection is currently underway.

Project title

The Saudi-Arab diseasome -a network of diseases: A comprehensive integrated network-based analysis using genomic, transcriptomic and proteomic data sets for identification of potential markers for diagnosis, prognosis, and therapeutic outcome for Saudi diseases, RAC# 2110 006, and under review for KACST Annual Research funding #PLB-Bi-MB-01 11-0148.

Investigators: D Colak, (PI), N Kaya, C Adra, AA Alaiya, M Dagestani, SM Amer, B Karakas, MM Shoukri

Project description

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

Progress

The project is currently under review for KACST Annual Research funding #PLB-Bi-MB-01 11-0148 and also submitted to ORA.

Project title

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

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

Project description

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

Progress

This project has been recently approved by KACST Biotechnology grant program.

Project title

Role of RORgt Transcription Factor in the Immune System Development, Autoimmunity and Transformation (Co-I) (grant from KACST) (RAC# 2080 046)

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

Project description

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

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

Project title

Wound Infection Rate and Risk Factors in Colorectal Surgery Patients at KFSH&RC-Riyadh Saudi Arabia. (RAC #: 2041071)

Principal Investigator: Denise Hibbert; BRU

Co-Investigators: 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.

Principal Investigator: Jameela Edathodu, MD; BRU

Co-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

Data are being collected.

Project title

Second Allogeneic Stem Cell Transplantation in Pediatric Patients at KFSH&RC, RAC #: 2081 098.

Principal Investigator: Mouhab Ayas, MD; BRU

Co-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 resulted from this project.

Project title

Impact of Laparoscopic Sleeve Gastrectomy on Iron Level and the Incidence of Iron-Deficiency Anemia., RAC #: 2071 047.

Principal Investigator: Hakeam A. Hakeam, MD; BRU

Co-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 #: 2091 069..

Principal Investigator: Zayed Al-Zayed, MD; BRU

Co-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

Data analysis completed.

Project title

Infection Risk with Noble-Metal Alloy Latex Urethral Catheters in Intensive Care Unit Patients

Investigators: Alaa Mukhtar, MD; BRU, Abdelmoneim 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 & nosocomial urinary tract infections rate in adult critical care units in King Faisal Hospital and Research Center.

Progress

In the data collection phase.

Project title

A Study of the Pathogenic Roles of HCV Infection in the Development of Postrenal Transplant Diabetes Mellitus, RAC #: 2071013.

Investogators: Ismail Ibrahim, MD, MRCP BRU

Co-Investigator: Abdelmoneim Eldali.

Project description

In spite of the considerable Progress in immunosuppressive and supporting treatment, numerous problems, which interfere with the success of renal transplantation, persist. Post-renal transplant diabetes mellitus (PTDM), a metabolic complication of renal transplantation, was originally described by Starzl in 1964. There neither is probably a single factor responsible nor is dose dependency of immunosuppressants involved.

Hepatitis C virus (HCV) infection represents an important problem for hemodialysis patients, and for those awaiting renal transplantation. There are some controversial reports about the role of HCV infection in the pathogenesis of PTDM in renal transplant recipients (4). A high prevalence of DM has been recently reported in patients with chronic HCV infection in the nontransplant population. HCV infection was associated with the development of PTDM, in addition to family history and increased age. The rate of autoantibodies against pancreatic cells was not increased in patients with HCV, which suggested that nonimmunologic mechanisms were likely to have a role in the pathogenesis of PTDM.

The main objective of this retrospective study is to assess the independent role of HCV infection and the underlying HLA genotype in the pathogenesis of PTDM.

The other specific aims are:

1. To identify the incidence of PTDM in renal graft recipients.
2. To recognize the interplaying risk factors of PTDM.
3. To focus on HCV infection as a risk factor and its plausible independent role in development of PTDM.
4. To assess the role of HLA genotype in predicting the development of PTDM in the subgroup of HCV-infected renal transplant recipients.

Progress

Data analysis completed.

Project title

Mercury Exposure During Lactation and Its Effects on Saudi Infant's Neurodevelopment. (BESC#: 001/2010, RAC#: 2080 049.

Principal Investigators: Dr Iman Al-Saleh and Dr Michael Nester; BRU

Co-Investigator: Wilhelmina Ventura

Project description

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

objectives of the study are: (1) to evaluate postnatal exposure to different forms of organic and inorganic mercury and its association with delayed neurological development at different age groups; (2) to identify a culturally relevant neurodevelopment assessment tool that can be used in a general practice settings; (3) to examine the extent of lactational transfer of mercury taking into account mercury speciation in order to have a critical assessment of its adverse health effects; (4) to test the role of oxidative stress due to mercury exposure on neurodevelopment defects in infants by measuring biomarkers such as urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) and malondialdehyde (MDA); (5) to compare different mercury exposure indicators in order to evaluate various forms of mercury exposure and their predictive validity for assessment of accurate biological monitoring. For example, blood and hair will be used to determine organic mercury, while urine is suitable to estimate elemental and inorganic mercury; (6) to identify sources of mercury exposure through the use of exposure-assessment questionnaires; and (7) to identify a cohort of infants with high levels of mercury for further studies in the future. This cross sectional study will recruit 1250 lactating Saudi mothers and their respective infants who have reached the ages of 3 to 12 months old during routine visits to their respective Primary Health Care Units in Riyadh. Different biological samples such blood, urine, hair and breast milk will be collected for mercury analyses using the Atomic Absorption Spectrophotometer, coupled to Vapor Generator Accessory. Infant developmental status will be assessed by the use of Denver Developmental Screening Test (DDST) which has four developmental dimensions: gross motor, fine motor-adaptive, language, and personal-social. The Parents' Evaluation of Developmental Status (PEDS) is another fast and inexpensive method for detecting developmental and behavioral-emotional problems will be also used which relies on parent's concerns about their infant's development. It is anticipated that this research project will provide relevant data to the public as well as health care community concerned with the impact of mercury on the health of young children especially with the recent concern over the use of thimerosal in vaccines and its possible association with autism and related disorders. Public health authorities could take the necessary legal and educational steps to restrict the availability of mercury containing products such as such as skin-lightening creams, thimerosal and dental amalgam.

Progress

Project was approved by KACSCT. Data collection form has been finalized and data collection is ongoing.

Project title

A Study to Examine the Concordance Between the Neuropsychology Data and the EEG, PET, and MRI Findings in the Pre-Surgery Evaluation of Epilepsy Patients, RAC#: 2061 080.

Principal Investigators: Dr Ahmed M. Hassan; Dr Abdulaziz Al-Semari, Dr Mona Al-Khawajah; BRU

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

Project title

Study of Demographic, Clinical, Pathological, Management, and Outcome Characteristics of Thyroid Cancer at KFSH & RC: A Retrospective Study. (RAC#: 2071 071; BESC#: 009/2008)

Principal Investigators: Ali Alzahrani, MD; Saud Al-Harthi, MD, Mohamed Al-Harthi, MD, Gamal Mohamed, PhD; BRU

Co-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 fo the study of the disease in all its aspects. A number of studies on the disease profile have been published from KFSH & RC but, was published around 10 years ago.

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

Progress

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

Project title

Gulf Center for Cancer Registration (RAC# 2061 022, BESC# 002/2006)

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

Project description

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

Progress

Rewrote/modified 14 programs that produce the population tree for different countries and age groups. The modifications were necessary to comply with the changes in the upgraded version of the software. Provide and explain program structure to a staff member. Ran population tree programs in SAS® for each GCC country. These charts are presented in the GCCR Annual/Cumulative Report.

Project title

Thromboembolic Disorders Registry (RAC# 2001 045, BESC# 004/2001)

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

Project description

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

Progress

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

Project title

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

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

Project description

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

Progress

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

Project title

National Family Safety Program, RAC# 2081 050, BESC# 008/2007.

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

Project description

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

Progress

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

Project title

Epilepsy Registry, RAC# 2011 059, BESC# 009/1997.

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

Project description

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

Progress

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

Project title

Neuromuscular Disease Registry (RAC# 2031 053, BESC# 010/1997)

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

Project description

The Neuromuscular Diseases Registry (NMDR) was established in 1998. It was discontinued in the same year to be resumed in September 2003. The registry is a coordinated collaboration between the departments of Neurosciences and Biostatistics, Epidemiology and Scientific Computing (BESC).

It is designed for the collection, processing, management and analysis of data on NMD patients. The nature and magnitude of these diseases are unknown in the Kingdom. Also their incidence and prevalence are also unknown, but the clinical impression had been that they are more prevalent in KSA than in any other countries. The NMDR at King Faisal Specialist hospital was established to provide health workers with a source of data on the epidemiology of neuromuscular diseases. Also to help them estimate the magnitude of the problem in the Kingdom, and to determine the types of neuromuscular diseases found in the population. Moreover, to obtain patterns of these diseases at KFSH&RC, identify associated risk factors, and to document diagnostic and treatment procedures. This registry is prospective with no sex, nationality, or age exclusion criteria.

Progress

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

Project title

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

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

Project description

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

Progress

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

Project title

Neural Tube Defects Registry, RAC# 991 029, BESC# 018/1999.

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

Project description

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

Progress

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

Project title

Saudi National Mental Health Servey, RAC# 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

Will be playing a double roll in the study: a data manager at first; during the data collection phase, and as a statistical analyst later when analysis begins. Attended 3 SAS analytical courses in preparation for providing statistical analysis for the project in the near future, and underwent vigorous training from the University of Michigan for my role as a data manger in the study.

OTHER WORK DONE ON NON-RAC APPROVED PROJECTS

Provided consultation on walk-in projects (Data Clinics) for the following departments:

- Comparative Medicine
- Biostatistics, Epidemiology, and Scientific Computing
- Department of Medicine

OTHER

- Provide technical assistance/guidance to staff on SAS related matters
- Solve online statistical analysis problems provided by SAS Enterprise Guide (EG) in preparation to provide SAS in-house training to end users, which includes writing a user manual on How-To-Use SAS EG; the point-and-click version of SAS

PUBLICATIONS OF THE BRU :

Books

- Shoukri, M.M., Measures of Inter-observer Agreement and Reliability, 2nd Edition. Chapman & Hall/CRC Press, Boca Raton, Florida. 260 pages, December 2010.

Peer reviewed journals

- Shoukri, M.M., Donner, A., Dessouky, N., Al-Mohanna, F. Estimation of Modified Concordance Ratio in Sib-Pairs: Effect of Consanguinity on the Risk of Congenital Heart Diseases, *International Journal of Biostatistics*, Vol 6 (1), 1-26, 2010.
- Ahmed, M. and Shoukri, M M. A Bayesian estimator of the intra-class correlation coefficient in beta-binomial sampling. *Journal of Data Science*. No (8) 127-137, 2010.
- Kottner, J., Streiner, D., Donner, A., Shoukri, M., Robert, C., Gajewski, B., Audige, L. Propsed guidelines for reporting reliability and agreement studies (GRRS). *Journal of Clinical Epidemiology 2010*: doi:10.1016/j.jclinepi.2010.03.002.
- Al-Alwan, I., Felimban, N., Altwaijri, Y., Tamim, H., Al-Mutair, A., Shoukri, M., Tamimi, T. Puberty onset among boys in Riyadh, Saudi Arabia. *Clinical Medicine Insight: Pediatrics*, 4: 19-24, 2010.
- Collison, K.S., Zaidi, M.Z., Subhani, S.N., Al-Rubeaan, K., Shoukri, M., Al-Mohanna, F. Sugar-sweetened carbonated beverage consumption correlates with BMI, waist circumference, and poor dietary choices in school children. *BMC Public Health*, 10:234 doi:10.1186/1471-2458-10-234, 2010.
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- Shoukri, M.M., Kumar, P. Colak, D. Analyzing Dependent Proportions in Cluster Randomized Trials: Modeling Inter-Cluster Correlation via Copula Function. *Computational Statistics and Data Analysis* (2010),doi:10.1016/j.csda2020.08.010.
- N Kaya, S Al-Muhsen, B Al-Saud, A Al-Bakheet, D Colak, A Al-Ghonaium , H Al-Dhekri, H Al-Mousa, R Arnaout, M Al-Owain, and M Iqbal, "ICF Syndrome in Saudi Arabia: Immunological, Cytogenetic and Molecular Analysis", *J Clin Immunol*, Dec. 2010.
- M Al-Dosari, R Shaheen, D Colak, F S Alkuraya, "Novel CENPJ Mutation Causes Seckel Syndrome", J of Medical Genetics, 2010 Jun;47(6):411-4.
- L. Al-Mansouri, Z. Shinwari, H. Ghebeh, M Pulicat, A. Tulbah, T. Al-Tweigeri, F. Al-Dayel, H. Al-Humaidan, D. Colak, A.A. Alaiya, and C. Adra, "Mapping the proteome of human breast cancer stem/progenitor cells: Towards discovery of stem cell specific biomarkers", HUPO 9th Annual World Congress, Sydney, Australia, 19-23 September 2010.
- Dilek Colak, Asmaa Nofal, Maimoona Nirmal, Hatim Jeprel, Namik Kaya, Al Bandary Al-Bakheet, Taher Tweigeri, Asma Tulbah, Dahesh Ajarim, Osama Al Malik, Suad M. Bin Amer, "Transcriptional profiling of breast tumors to identify age-specific signatures and molecular characterization of cancer Progression in Saudi females", International Symposium on New Frontier in Breast Cancer, 27-29 April 2010.
- Mohammed Dehbi, Engin Baturcam, Abdelmoneim Eldali, Maqbool Ahmed, Aaron Kwaasi, Muhammad Azhar Chishti, Abderrezak Bouchama.. Hsp-72, a candidate prognostic indicator of heatstroke. *Cell Stress and Chaperones*, 2010 Feb 23.
- Alghamdi, Saad A.; Nabi, Zahid G.; Alkhafaji, Dania M.; Askandrani, Sumaya A.; Abdelsalam, Mohamed S.; Shoukri, Mohamed M.; Eldali, Abdelmoneim M.; Adra, Chaker N.; Alkurbi, Lutfi A.; Albaqumi, Mamdouh N. Transplant Tourism Outcome: A Single Center Experience. *Transplantation*, May 2010.
- Maha H Daghestani, Arjumand Warsy, Mazin H Daghestani, Ali N Al-odaib, Abdelmoneim Eldali, Nadia A Al-Eisa and Sabah Al-zhrani. The Gln27Glu Polymorphism in Beta 2-Adrenergic receptor gene is linked to hypertriglyceridemia, hyperinsulinemia and hyperleptinemia in Saudis. *Lipids in Health and Disease*, 25 August 2010.

TRAINING

- Summer Training Lectures.
- Biostatistics from the Beginning.
- Biostatistics Research Methods course.
- Business Mathematics course for Medical Secretaries Program.

Epidemiology Research Unit

Head

Yasmin Al Twaijri, PhD

Members

Ali Al Zahrani, MD, PhD
Ravichandran Kandasamy, PhD
Maha Al Eid
Amal Al Madouj
Batlah Al Murshed
Abdulrahman Bin Muammar
Mansour Al Joufan, MD (Joint Appointment)
Saud Al Shanefey, MD (Joint Appointment)
Mona Shahab (Visiting Staff from PSCDR)
Feda Altuwaijri (Visiting Staff from PSCDR)
Bilal Sohail (Visiting Staff from PSCDR)

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.

Project Title

Saudi National Mental Health Survey, RAC# 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, Mohamad Basolaiman, Khaldoon Marwa, Majid Desouki, Ron Kessler, Beth-Ellen Pennel, Ali Alzahrani, Naseem Qureshi

Project Manager: Mona Shahab (PSCDR)

Project Coordinator: Feda Al Tuwaijri (PSCDR)

Research Coordinator: Maha Al Eid

Programmers: May Al Husseini, Mansour Baig, Lyna Al Fantoukh (TDBCF Unit)

Helpdesk Team: Bilal Sohail, Mashnoof Alrowaily, Arnie Tayco (CSCF Unit)

ACASI Team: Abdulrahman bin Muammar, Batlah Murshid

Data Manager: Samia Alhashem (Biostatistics Unit)

IT (Genetic data): Faris Abumelha (Genetics Dept.)

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

Several rounds of meetings with Ministry of Health and Ministry of Economy and Planning officials were conducted, which culminated in drafting Memorandums of Understandings between the institutions and PSCDR. Pretesting of the CIDI instrument has been completed. Several new sections have been developed and added to the Saudi version of the CIDI (Dementia, disability, psychosis, religiosity, women health), SCID training (Structured Clinical Interview for DSM Disorders) was given by Dr. Michael First, one of the developers of the SCID interview in Columbia University, NYC and was attended by Ms. Shahab and Dr. Dessouki, followed by 3-day training of the SCID interviewing team in Riyadh by Dr. First. An online database for SCID interviewers is currently being designed and developed by Ms. Shazia Subhani and Ms. Bushra Siddiqui. Study Programmers attended 2 week training visits at Harvard University and University of Michigan during the summer of 2010. Programming of the Arabic CIDI interview into the Blaise software has been completed and is being tested. All ACASI audio recordings have been recorded at the A/V department and have been programmed into the Blaise program.

Helpdesk staff received live web training by our collaborators in the WHO-World Mental Health Data Collection Center at the University of Michigan Ann Arbor, and we are currently setting up the Helpdesk center. A Calling Center with toll-free 800 number has been created for the project in collaboration with the KFSH&RC Department of Safety, Security and Communication. This toll-free number will be used to receive calls for the Helpdesk and for project staff. Call management and statistics will be enabled. Preparations for the Pilot test are underway, and equipment has been purchased. A portion of the DNA saliva kits have been purchased and coordination with the Genetic department is underway. Ms. Samia Al Hashem attended several advanced SAS programming courses in USA, and has been attending a personal web based training seminar with the data manager at Harvard University's WHO World Mental Health Data Analysis Center.

Project title

Riyadh Puberty Study, RAC# 2081 020.

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

Project description

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

Progress

1. Descriptive data analysis has been completed.
2. Analysis of the data from the boys and girls was conducted, with a result of publication of two manuscripts.

Project title

Knowledge, Awareness and Attitude About Cancer and Its Prevention, RAC# 205 1041.

Invistigators: 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# 991 030.

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

Project description

The King Faisal Specialist Hospital and Research Centre (KFSH&RC) established a Cleft Lip/Palate (CLP) registry and started collecting data on CLP 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 CLP registry is expanded in year 2002 to include Craniofacial Anomalies (CFA) 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

Over the twelve year period (1999-2010) this registry registered a total of 1,418 cases (M=783; F=635). Out of the 1,418 cases registered so far, 933 cases had only CLP, 160 cases had only CFA and another 325 cases had both CLP and CFA. Among CLP patients' cleft palate was most common followed by unilateral cleft lip and palate and bilateral cleft lip and palate. Overall, the male to female ratio is 1.25:1. Out of the 485 total craniofacial patients there were 263 male and 222 female cases with a male to female ratio of 1.18:1. There were 1,362 Saudis (M=757; F=605) and 56 Non-Saudis (M=26; F=30). Most of the cases were from Saudi Arabia (1401; 98.8%) and only 17 (1.2%) cases were from outside Kingdom. Out of the 13 administrative regions of Saudi Arabia, Riyadh region had more number of cases (428; 30.5%) followed by Asir (202; 14.4%) and Eastern (193; 13.8%) region. More than half of the patients (M=454; F=328) parents were consanguineously married. The parental consanguineous status was not available for 45 patients (M=27; F=18). Family history of orofacial deformities was reported by 399 (28.1%) cases and for 43 (3.1%) cases the information was not available. Out of the 399 cases reported having a positive family history, 212 were male and 187 were female. Out of the 804 initial lip & nose repair 618 (76.9%) were done at KFSH&RC and out of 892 initial palate repair 741 (83.1%) were done at KFSH&RC.

A report, 'Cleft Lip/Palate and Craniofacial Anomalies Registry: Annual Report 2009' was published. An article entitled, 'Pattern of craniofacial anomalies seen in a tertiary care hospital, Riyadh, Saudi Arabia' was accepted in a peer reviewed journal.

Project title

Modeling Familial aggregation of cleft lip/plate: A hospital based registry study. (RAC# 2101 004)

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

Project description

Several studies have shown that certain birth defects are known to recur in families and the risk of having an infant with a birth defect varies among women. But only few population-based studies estimated risk of recurrence for birth defects in subsequent sibs among consanguineous parents. The risk of recurrence of birth defects is higher for subsequent sibs with first-cousin parents than for those with non-consanguineous parents. The risk estimates for the recurrence of cleft among first-degree relatives (defined as the prevalence of clefting in first-degree relatives compared with the population prevalence) ranges from 24-fold to 82-fold. Given the uncertainty about the causes of clefts, the tendency for clefts to recur in families is striking. Little is known about the influence of consanguinity on oral cleft in Saudi Arabia. The objectives of this study are to assess the possible effects of consanguinity on the occurrence of cleft lip or cleft palate or both (CLP) and the recurrence of these clefts among subsequent sibs.

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

Progress:

Of 1,171 total patients, CL±P was found to be more common (64.0%) than CP (36.0%). Male predominance in CL±P (1.5:1) and a female predominance in CP (0.9:1) was observed ($p<0.0001$). Family history of clefts was observed in 30.5% of the patients and CL±P patients had more history than CP patients (33.6% vs. 22.0%; $p<0.0001$). Among first-degree relatives, siblings of the patient were mostly affected (siblings: 147, fathers: 27, mothers: 8). Consanguineous marriages was seen in 54.4% of our patient's parents. More history of orofacial

cleft was seen in the family of patients whose parents were consanguineously married than non-consanguineously married (34.2% Vs. 25.8%; p=0.003); and the significance persists both among the CP and CL±P group. Recurrence among siblings was not different from those of consanguineous and non-consanguineous marriages. Of the 35 parents born with CLP, only 16 (45.7%) had a consanguineous marriage and for one couple (2.9%), the status was unknown. Recurrence of cleft in offspring was higher among parents who had cleft than those who did not have it (51.4% vs. 11.4%; p<0.0001); and this difference persists in both CL±P and CP group. The formulation of a public health program including education about the anticipated genetic consequences is a necessity in this population with a high degree of consanguinity.

Results of the study were presented in the 3rd International cleft palate and craniofacial symposium, KFSH&RC, Riyadh, March 2011. A manuscript entitled, 'Consanguinity and Occurrence Pattern of Cleft Lip/Palate: A hospital-based registry study in Riyadh' was submitted to a peer reviewed journal.

Project title

Spatial-temporal analysis of breast cancer incidence in Saudi Arabia (RAC# 2101 008)

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

Project description

Incidence of cancer may vary within a country and overtime because of previous differences in exposure to risk factors or the introduction of new diagnostic methods or interventions for early detection. Limited number of studies assessing regional, state-specific, county and even small area cluster investigations has been performed in order to assess geographic variations of breast cancer. 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 examines whether observed geographic variations in breast cancer incidence are random or statistically significant and whether the statistically significant excesses areas are temporary or time-persistent. 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.

Progress:

All invasive breast cancer cases diagnosed between 1994 and 2005 among Saudi women (n=8242) were included in this study. Patient's usual address of residence was used when they are aggregated to a geographical unit. There were 43 areas with more than 15 cases over the study period. Riyadh had more number of cases (1,886) followed by Jeddah (1,491), Ahsa (542) and Makkah (528). Areas like Afif, Samath and Qoweyeiya had only 16 cases over study period. The poison regression model based on number of cases within each region/area was used to estimate the parameters. Age (as continuous variable) and year of diagnosis (categorical variable) were included as a covariate. The variance estimated (region=0.02431 and city within region=1.52) by Generalized Linear Mixed Models with compound symmetry correlation structure shows most of the variability in the data is from variability among cities. Further analysis is in progress.

Project title

Questionnaire to explore the Knowledge, Perception, and Attitude of cancer patients towards cancer and cancer treatment, who are under treatment at King Faisal Specialist Hospital And Research center, RAC#2101 056.

Investigators: Ali Aljubran, Ahlam Haddad, Fatima Almarhoon, Kandasamy Ravichandran, Sara Almassaad, Anas Al-Qesiyeh

Project description

Understanding the attitudes of cancer patients towards different cancer related issues is very important for the health care provider in order to deliver an optimal care. However, in Saudi Arabia there is yet no clear knowledge about the patient's preferences or attitudes towards, for example, the disclosure of information, use of complementary and alternative medicine (CAM) or the support provided by the society organizations.

This study is intended to explore the Knowledge, perception, and attitude of cancer patients who are under treatment at King Faisal Specialist Hospital towards cancer and cancer treatment. The specific objectives of the study are: *i*. to determine the patient's attitude towards disclosure of the cancer diagnosis

and prognosis, *ii*. to examine the trend of use of CAM in cancer patients, and their attitudes towards CAM, *iii*. to know the patients impression about the support provided by their families or the non- governmental organizations "NGOs", *iv*. to know the patients sources of knowledge and information about their diseases, and *v*. to find the relation between the various demographic, educational and social factors as well as the disease factors with the patients attitudes.

Progress

A Questionnaire developed in English was translated to Arabic to acquire data from adult patients with established diagnosis of cancer and who attend the outpatient medical oncology clinic. Data collection was completed with 250 subjects, the required sample for this study. Coding and back translation of information (to English) is in progress. To understand the background of the different aspects of the patient's attitudes, the results will be analyzed against the various patient's demographic, educational, social and disease factors.

Project title

Impact of Tube Feeding on Aspiration Pneumonia, RAC# 2091 061.

Investigators: Muneera Al-Bugami, Yasmin Altwaijri

Project description

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

Aspiration pneumonia (AP) is a common cause of respiratory morbidity and mortality in elderly and debilitated patients *(1)*. 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 *(2-4)*. 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 *(5)*.

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 *(6,8,9)*.

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 *(7, 8)*.

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

The Data Abstraction Form was modified to incorporate suggestions of the research team. The physicians who will be

involved in data collection from the patients' medical records have met with the PI and study objectives have been discussed. Approval to access patents' files has been received by the Medical Records department. Data Collection has begun.

Project title

Metabolic syndrome prevalence among childhood acute lymphoblastic leukemia (ALL) patients after the end of treatment, RAC# 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# 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# 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 Center 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# 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

Incidence, Risk Factors and Severity of Hypoxic-Ischemic Encephalopathy in Saudi Arabia: A national Epidemiologic Study, RAC# 2101 015.

Investigators: Dr. Saleh Al-Alaiyan, Dr. Ali Al-Zahrani

Project description

Hypoxic ischemic encephalopathy (HIE) – insufficient oxygen supply – can lead to severe hypoxic ischemic organ damage in newborns followed by a fatal outcome or severe life-long pathologies. Although asphyxia is not always distinguishable as the cause of prenatal and perinatal death its pronounced impact for the mortality in newborns is well-documented, representing the pathology as a profound deficit in the current health systems worldwide. Reliable statistics should ideally be based on national surveillance, unfortunately all data about HIE in Saudi Arabia have been driven entirely from hospital-based statistics, which are bound to be inaccurate and does not represent the overall incidence at the national level. In addition, data from Saudi Arabia reflect the rate of the disease in some hospitals in the region.

As a result of limited data, the incidence of HIE in Saudi Arabia is unknown and so are the predisposing risk factors. The objective of our national prospective cohort study is to assess the incidence, risk factors and the severity of HIE in Saudi Arabia in order to accurately measure the magnitude of this problem and its direct predisposing factors and then propose a national plan of some preventive and therapeutic interventions to limit the impact of HIE on health care in Saudi Arabia.

Progress

Study proposal has been approved by ORA, CFR's we designed and tested, waiting for fund approval from KACST.

Project title

Perceptions of Saudi Parents on the Participation of their Infants in Clinical Research (RAC# waiting for approval).

Investigators: Dr. Saleh Al-Alaiyan, Dr. Mohamed Shoukri, Abdulrahman Bin-Muammar, CCRP, MBA

Project description

Good neonatal research is essential if we are to improve the care and outcome of newborn premature infants. Vital research in newborn infants may be being stifled through misplaced fears of causing parents stress by asking them to permit their infant's entry into clinical trials.

To improve pediatric medical care, it is important to perform research studies and interventions with children that do not offer a compensating potential for clinical benefit. (1-3) Guidelines around the world allow children to be involved in such nonbeneficial research when the risks are minimal.(4-6) Nonbeneficial pediatric research continues to be subject to intense theoretical debate,(6-9) and some commentators argue that it is unethical to expose children to research risks for the benefit of others. Evaluation of this debate should include data on the attitudes of those most affected, namely, children and their parents. One might assume that children and parents accept nonbeneficial pediatric research, as children often participate. Yet, children and parents may agree to the child's participation because they endorse some nonbeneficial pediatric research or because they fail to recognize that it does not offer a compensating potential for clinical benefit.

It is normal practice for informed consent to be obtained from parents for research on newborn infants. For consent to be valid, parents must be deemed to be mentally competent, to have received appropriate information, to be able to understand the information, and to give consent voluntarily. Increasing rates of parental refusal to enroll their infants in clinical trials have been cited as evidence that parents often do not understand the importance of research. Negative media attention may also bias parents against the research process. When clinical trials suffer poor enrollment rates, studies may be canceled, take much longer to conduct, cost considerably more, or fail to answer the research question. This significant impediment to essential scientific investigations has been termed the "crisis in pediatrics".

Progress

CFR's we designed, Study proposal has been sent to ORA for approved.

What is the Hydration status of Emergency Department Physicians and Nurses by the end of their shift (RAC# waiting for approval)

Investigators: Dr. Mohammed Alomar, Dr. Mohamed Shoukri, Abdulrahman Bin-Muammar, CCRP, MBA

Project description

The typical shift of ED physicians and nurses is not only cognitively demanding, requiring complex decision making in a fast-paced environment, it is also physically demanding. During their shift, ED physicians may be far removed from areas that provide access to fluids and when it's available cannot keep it handy for the of infection control purposes. As a result, physicians are often unable to drink properly or at all during their shifts. No other substance important to our body than water. It's the major component of our blood and urine. Previous studies have demonstrated that the impairment of neurological functions such as fine motor skills, information processing, and memory, is linked to hypoglycemia and under-nutrition and may contribute to motor vehicle collisions and air crashes [1-5]. Conversely, sport scientists have demonstrated that optimized nutrition can sustain work output and concentration over extended periods of high physical and mental stress with great success. These techniques have been shown to improve health and wellness in occupational groups such as tree planters and heli-ski guides [6-9]. Physician performance has been increasingly linked to lifestyle and wellness factors such as sleep deprivation and stress and, in turn, to the quality of patient care [10-14]. Physicians are often unable to drink properly during their shift and we feel they are not enough hydrated. However, there is a lack of research that empirically examines the hydration status of ED staff during their shifts. The objective of this study is to examine the hydration status of ED staff by the end of their shifts. Good hydration may ultimately benefit not only the physicians and nurses themselves but also their patients and the health care systems in which they work [15-17]. Compare to the beginning we aim to assess the hydration status of the ED physicians and nurses by the end of their shift.

Progress

CFR's we designed, Study proposal has been sent to ORA for approved.

Computing Services Core Facility

Head

Parvez A. Siddiqui

Members

Mashnouf Al Rowaily
Arnie Tayco
Yousef Hussain
Michael Edquiban (RC Grant Employee)
Bander Al Khodairy (Scholarship Leave)

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.

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.

Title	Date
Attend HDES Symposium NLNBS: Lifecycle, Autodelfie, and Victor (software) Training at Perkin Elmer in Finland	21 March 2011
Training for Helpdesk to support Saudi Mental Health Disease Survey Pilot Study attended by Arnie and Mashnouf	August 2010 – April 2011
Scholarship	Mr. Bander AlKhodairy

Courses Attended by CSCF Staff members.

Seminars/Workshop Title	Date
Netwok A+	
International Conference on Radiation Medicine	1-4 March 2010
Saudi Conference on Medical Physics	19 October 2010
Fourth Annual Research Day	19 January 2011
Japanese – KFSH & RC Oncology Seminar	02 March 2011
Health Decisions Made Easy Symposium	21 March 2011

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 2010 CSCF setup new PCs, laptops, workstation, printers, servers and other major computer peripherals. The CSCF was successfully installed and configured three servers will be used by Registry Core facility to help them to develop state of art registry applications.

CSCF setup and configured	
60	new PCs and distributed to assigned departments
6	new laptops
9	new black and white printers
9	new color printers
18	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:

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

Helpdesk

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

Configuration and Distribution

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

Summary of the calls per department logged by CSCF during the year 2010

Department	No. of Logged Calls
BESC	418
BMP	231
BMR	315
CCR	125
CMD	134
CPPEO	101
C&R	140
Genetics	117
ORA	99
RC-Admin	80
Stem Cell Therapy	168
T&E	67
KFNCCC-Research (CDU)	74
KFNCCC-Research (SDL)	80
KFNCCC-Research (HCGL)	110

Registries Core Facility

Head

Shazia Naz Subhani, MSc

Members

Nadia Dessouky MD
Ahsan Yaseen MPH
Najah Aftab Siddiqui M.Sc
Ebthisam Al-Jarba BA
Ehsan El-Shamy BSN
Rozeena Huma MD
Hanaa Abdulghany BS
Hala Al Assiry BA
Nada Bawyan
Najah Finjan
Saleh Abdulkadir Saeed
Abeer Al Firm

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.

Throughout the year 2010, registries scope has expanded not only in terms of national collaborations but also in terms of planning and developing new registries namely Cystic Fibrosis Registry, Hip Registry, Breast Cancer Registry and Diabetes Registry for KFSH&RC. Currently, RCF is administering several hospital based, regional and national registries. Members of RCF were involved trainings users from various collaborating hospitals on regional and national level. Data recorded and reported from individual registries were tabulated and presented as cumulative and/or annual reports. All reports are available under a common link http://rc.kfshrc.edu.sa/rcf. Comprehensive electronic libraries for individual registries were created and uploaded for reference under the same link. Several data requests for the spin-off projects, after necessary documentation, were furnished to researchers. Several presentations on the research projects were made along with co-authorships on research papers. The presented work for the registries on national and international levels were awarded and recognized.

Additionally, in 2010 the effective use of health care technologies lead several registries to get projected; using published data; on the dynamic health statistics platform. KFSH&RC is a pioneer in the establishment of disease registries and keeping in view the strategic planning for research activities efforts are in place to bring all published registries data under this dynamic platform. The dynamic platform will enhance the importance of research data collected over the years for the on-going registries by providing instant tabulations, graphs and maps. This will not only satisfy the research inquiries but will also play a major role in the administrative decision and public awareness for various health problems addressed through the registries. The platform is accessible under http://altabari.kfshrc.edu.sa.

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.

RESEARCH PROJECTS

Project title

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

Investigators: Zohair Halees MD, Mansour Al Jufan MD, Futwan Al Mohanna Ph.D, Mohamad Shoukri Ph.D, Ahmad Omrani MD, Shazia Naz Subhani M.Sc, Nadia Dessouky MD

Project description

The congenital heart defects registry of the King Faisal Specialist Hospital and Research Centre (KFSH &RC) was established in 1998 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 – 2010) submitted.
- Progressive Collaborations
  King Faisal Specialist Hospital and Research Center, Jeddah joined the collaboration on July 2010
- Presentations
  "Features and Concepts: Saudi Congenital Heart Defects Registry", Poster Presentation during the 44th scientific meeting of the Association of the European Pediatric Cardiology, 26-29 May, 2010, Austria

Statistics for all year cases as of December 31, 2010 is:

Collaborating Hospitals	New cases	Follow up cases	Diagnosis coding	Treatment coding
(KFSH&RC, PSSC, Dammam Maternity & Children Hospital)	19,870	46,884	16,313	18,540

Statistics for year 2010 is:

Collaborating Hospitals	New cases	Follow up cases	Diagnosis coding	Treatment coding
(KFSH&RC, PSSC, Dammam Maternity & Children Hospital)	1631	3788	1139	1537

PUBLICATIONS

- Multi-Institutional Cumulative Report (1998 – 2009)
- Estimation of Modified Concordance Ratio in Sib-Pairs: Effect of Consanguinity on the Risk of Congenital Heart Diseases, Mohamed M. Shoukri, Allan Donner, Nadia Abdalla Dessouky, Shazia Subhani, Mansour Al-Joufan, Ahmed Al-Omrani, Futwan Al-Mohanna, And Zohair Y. Al Halees, *The International Journal of Biostatistics*. Available at: *http://www.bepress.com/ijb/vol6/iss1/3*.

Project title

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

Investigators: Essam Al Shail MD, Mohammad Al Abdulaaly MD, Zayed Al Zayed MD, Mohamad Shoukri Ph.D, Hoda Kattan MD, Wesam Kurdi MD, Nadia Sakati MD, Shazia Naz Subhani M.Sc , 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.
- Burden of the Disease for the NTD cases was estimated using the registry data and presented to the H.E. Minister of Health.
- On-going collaboration with regional hospitals
- Statistics for all year as of December 31, 2010 is:

	New cases	Follow up
Collaborating Hospitals	643	323

- Statistics for year 2010 is:

	New cases	Follow up
Collaborating Hospitals	42	53

FUTURE DIRECTIONS

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

PUBLICATIONS

Eighth Annual Report with Registrations from October 01, 2000 till December 31, 2009.

Project Title

Epilepsy Registry, RAC #: 2011-059.

Investigators: Abdulaziz Al Semari MD, Aziza Chedrawi MD, Hisham Al Dhalaan MD , Ibrahim Thubaiti MD, Salah Baz MD, Suad Al Yamani MD, Shazia Naz Subhani M.Sc , Najah Aftab Siddiqui M.Sc.

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:

1. Intractable Epilepsy and Functional Hemispherectomy: a report of 41 cases" I. Thubaiti, A. Alsemari, T. Abalkhail, S. Alyamani, A. Chedrawi, H. Aldhalaan, S. Baz. 2nd East Mediterranean Epilepsy Congress. Dubai, March 2010.
2. "Demographic profile of patients with epilepsy" A. Alsemari, S. Baz, I Thubaiti, S. Alyamani, A. Chedrawi, T. Abalkhail, H. Aldhalaan. 2nd East Mediterranean Epilepsy Congress. Dubai, March 2010.
3. "Epilepsy in Older People from a Tertiary Care Centre in KSA" S. Baz, A. Alsemari, T. Abalkhail, I. Althubaiti. 2nd East Mediterranean Epilepsy Congress. Dubai, March 2010.
4. "A review of our experience in the pre-surgical evaluation of epilepsy patients with invasive EEG recording" A. Alsemari, S. Baz, I Thubaiti, S. Alyamani, A. Chedrawi, H. Aldhalaan. 2nd East Mediterranean Epilepsy Congress. Dubai, March 2010.
5. "CNS tumours and refractory epilepsy: surgery outcome in a tertiary care centre" T. Abalkhail, S. Baz, I Thubaiti, S. Alyamani, A. Chedrawi, H. Aldhalaan, A. Alsemari, 2nd East Mediterranean Epilepsy Congress. Dubai, March 2010.
6. "A look at temporal lobe epilepsy surgery experience in a tertiary care centre in KSA" S. Baz, I Thubaiti, T. Abalkhail, S. Alyamani, A. Chedrawi, H. Aldhalaan, A. Alsemari,. 2nd East Mediterranean Epilepsy Congress. Dubai, March 2010.
7. " Vagal Nerve Stimulation as an adjunctive therapy for refractory epilepsy" S. Baz, I Thubaiti, T. Abalkhail, S. Alyamani, A. Chedrawi, H. Aldhalaan, A. Alsemari. 2nd East Mediterranean Epilepsy Congress. Dubai, March 2010

8. "Diagnostic value of WADA in lateralization of Arabian patients temporal lobe epilepsy" E. Ibrahim, A. Izzeldin, A. Alsemari, S. Baz, I. Thubaiti, A. Chedrawi, T. Abalkhail. 2nd East Mediterranean Epilepsy Congress. Dubai, March 2010.
9. Do we need driving regulations for patients with epilepsy in East Mediterranean countries?
   a. The second ILAE , IBE, East Mediterranean Epilepsy Symposium March 2010 –Dubai
10. Demographic profile of patients with epilepsy. -.The second ILAE, IBE, East Mediterranean Epilepsy Symposium March 2010 –Dubai.

Statistics for all year as of December 31, 2010 is:

	New cases	Diagnosis	Surgery
Collaborating Hospitals	3747	2772	535

Statistics for year 2010 are:

	New cases	Diagnosis	Surgery
Collaborating Hospitals	245	310	46

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 (2009)

Project Title

Cleft Lip / Palate and Craniofacial Anomalies Registry (CLCPR) RAC#: 991-030

Investigators: Aziza Al Johar MD, Essam Al-Shail MD, Abdulaziz Al Rubaiya MD, Kandasamy Ravichandran Ph.D, Shazia Naz Subhani M.Sc , Ebthisam Al Jarba BA

Project Description

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

Progress

- Data validation and auditing.
- Presentations on registry data as follows:
  - Consanguinity and Occurrence Pattern of Cleft Lip/ Palate: A hospital-based registry study, Riyadh
  - Review Craniosynostosis cases by Dr.AlShail and Dr.Anwar UL Haq

Statistics for all year as of December 31, 2010 is:

	New cases	Diagnosis coding	Treatment coding
King Faisal Specialist Hospital & RC	1418	1459	1456

Statistics for year 2010 are:

	New cases	Diagnosis coding	Treatment coding
King Faisal Specialist Hospital & RC	101	323	447

FUTURE DIRECTIONS

Collaborations

PUBLICATIONS

- Annual Cleft Lip/Palate and Craniofacial Anomalies Registry Report 2009.

Project title

Thromboembolic Disorders Registry (TEDR) RAC#: 2001045

Investigators: Abdulaziz Al Harthi MD, Jalal Saour MD , Habib Bassil MD, Layla Mammo MD, Mohamad Shoukri Ph.D, Mansour Aba Al Khail MD, Mustafa El Naggar MD, Mona. El Sherif MD, Shazia Naz Subhani M.Sc , 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, 2010 is:

	New cases	Follow up cases
King Faisal Specialist Hospital & RC	3190	4535

- Statistics for year 2010 is:

	New cases	Follow up cases
King Faisal Specialist Hospital & RC	276	851

Publications

- Thromboembolic Disorders Registry Cumulative Report (2001 - 2009).

Project Title

Venous Thrombosis and Thrombophelia Disorders Registry (VTFT) RAC#: 2001 017

Investigators: Jalal Saour MD, Layla Mammo, Mohamad Shoukri Ph.D, Shazia Naz Subhani M.Sc, 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 Center 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

- Collaboration invitations to major hospitals in KSA
- As of December 31, 2010 total counts in the database is: 1363 cases
- For year 2009 patients registered are: 136 cases

FUTURE DIRECTIONS

National collaborations

Project Title

Neuromuscular Disease Registry (NMDR) RAC#: 99 1029E

Investigators: Mohammed Al Muhaizea MD, Saeed Bohlega MD, Bent Stigsby MD, Hisham Al-Dhalan MD, Shazia Naz Subhani M.Sc , 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

- Data provided for 2nd Saudi International Pediatric Neurology Meeting.
- Presentation titled Title: "Duchenne Muscular Dystrophy" given in King Fahad Medical City
- Presentation at the 1st International Conference for Neuromuscular Diseases. Title: "Neuromuscular Diseases in Saudi Arabia Glimpse from the NMD Registry".
- Data audited prior to cumulative report data tabulation.
- Statistics for all year as of December 31, 2010 is:

	New cases	Diagnosis coding	Treatment cases
KFSH&RC	2442	2442	2826

- Statistics for year 2010 are:

	New cases	Diagnosis coding	Treatment cases
KFSH&RC	368	368	376

PUBLICATIONS

Neuromuscular Disease Registry 2010 Annual Report.

Project title

National Diabetes Registry (RC Administration-approved)

Investigators: Khalid Rubean MD, Mohamad Shoukri Ph.D., Shazia Naz Subhani M.Sc

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 28 hospitals) from all over Riyadh region.

Presentations

- S. Subhani, "Health Decisions Made Easy" using Diabetes as a model in ESRI Health GIS 2010 Conference, Denver, Colorado, USA
- Several Lectures given in the "Diabetes Educators Courses"

FUTURE DIRECTIONS

Collaboration expansion on National Level

PUBLICATIONS

- Shazia Subhani, Khalid Rubean. "Design and Development of a Web-Based Saudi National Diabetes Registry". Journal of Diabetes Science and Technology Volume 4, Issue 6, November 2010

Project title

National Family Safety Registry (NFSR) RAC#: 2081 050

Investigators: Huda Kattan MD, Maha Muneef MD, Majid Al Eissa MD , Shazia Naz Subhani M.Sc.

Project description

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

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

Progress

1. IPPs, Bylaws completed and implemented.
2. Successful implementation of the web-based registry application with on-site trainings to users across the 38 centers of the Kingdom.
3. Total of 305 cases registered in the centralized database from across the Kingdom.
4. First Report on the National Family Safety Registry completed.

FUTURE DIRECTIONS

Collaborations with Ministry of Social Affairs and other hospitals.

Publications

First Report on National Family Safety Registry

Project title

Pan Arab Liver Transplantation Registry (PALTR) RAC #: 2071 022

Investigators: Professor Mohamed Al-Sebayel MD, Hatem Khalaf MD, Khalil Alawi M.B.B.S, Mohamad Shoukri Ph.D , Shazia Naz Subhani M.Sc

Project description

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

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

Progress

1. On-going collaboration with Wade-e-Nyle, Egypt and Cairo University, Egypt.
2. As of December 31, 2010 a total of 620 patients registered in the centralized database.
3. On-going data collection and entry in the registry database.

FUTURE DIRECTIONS

Pan Arab Level Collaborations.

Project title

Rare Dental Disorders Registry (RDDR) RAC#: 2071 082

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

Project description

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

disorders to get adequate information, diagnosis and treatment at King Faisal Specialist Hospital & Research Center.

Progress

1. Registry web application design under testing phase with dummy data.
2. Data capturing is prospective by the registry members for later registration in the database.

FUTURE DIRECTIONS

Collaborations.

Project title

Primary Immunodeficiency Registry (PIDR) RAC#: 2081 111

Investigators: Bandar Al Saud MD, Saleh Al Muhsen MD, Abdulaziz Al-Ghonaium MD, Hmoud Al-Musa MD, Hasan Al-Dhekry MD, Sulaiman Al-Gazlan MD, Hasan Al-Rayes MD, Rand Arnaout MD, Nazeema Elsayed, Mohamad Shoukri Ph.D , Shazia Naz Subhani M.Sc.

Project description

Primary immunodeficiencies are disorders in which part of the body's immune system is missing or does not function properly. To be considered a Primary Immunodeficiency, the cause of the immune deficiency must not be secondary in nature. About 1 in 500 people is born with a primary immunodeficiency (Wikipedia).

Since PIDD are complex and chronic lasting from birth through adulthood and requiring long term coordinated treatment, it was particularly important to have a registry for this disease. Seeing the necessity, KFSH&RC designed a registry for this purpose in the year 2010to provide a database on PIDD patients at the hospital and use the data collected to enhance patient care by justifying the allocation of resources based on need.

Progress

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

Statistics for all year as of December 31, 2010 is:

	New cases	Diagnosis coding	Treatment Coding
KFSH&RC	238	238	238

FUTURE DIRECTIONS

National Collaborations

Technical Databases Core Facility

Head
Saleh Al Aqeel

Members
Bushra Siddiqui
May Al-Husseini
Lyna Al-Fantoukh
Fahad Al-Enazy
Mansoor Baig

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

APPLICATIONS

Developed / Being-developed in 2010

Primary-Immuno Deficiency Registry

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

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

Rare Dental Disorders Registry

The Rare Dental Disorders Registry (RDD) of the King Faisal Specialist Hospital and Research Centre (KFSH & RC) was established in 2010 as a collaborative effort between the Department of Biostatistics, Epidemiology and Scientific Computing and the Department of Dentistry.

The registry aims in collecting patients with the following disorders:

- Ectodermal Dysplasia
- Papillon-Lafevre syndrome
- Amelogenesis imperfecta
- Dentinogenesis imperfect
- Cleidocranial dysplasia
- Hypodontia/aplasia

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

NewBorn Screening – Results System

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

Saudi Heart Association Membership Management. System

The Saudi Heart Association had a requirement to have a membership management system where they can store all the member details which will be updated by the doctor or the administrator on a timely basis. The administrator would be able to add new members and assign them the login privileges, the members would then be able to log on to the system and update their profile or upload membership renewal documents. It also covers reporting, search and custom list for expired memberships.

PHASE 2 : will cover the automatic email generation on and before any membership expires., this will be covered soon. It has been developed using the .NET platform with SQL server as the backend database.

APPLICATIONS RE-DEVELOPED

New Versions -2010

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 application on a ASP. NET or Enhance the applications to include more dynamic capabilities using AJAX.

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

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.

Medical Second Opinion

This project is for the Health Outreach Services Office. Data for Patients requesting Medical Second Opinions will be entered into this application for reporting and Analysis.

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

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

APPLICATIONS

Modified during year 2010

Congenital Heart Defects Registry

The Congenital Heart Defects Registry is a registry designed for the collection, management, and analysis of data on CHD 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

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.

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.

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. These are 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)

The Thermo Luminiscent Dosimetry (TLD) Database Application of 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 New Born 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.

PROFESSIONAL TRAINING

TDBCF Trainees

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

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

Summer program 2010

TDBCF provided summer training for two students from Ibn Sena Program.

Objectives

- Understand programming and relational database concepts
- Develop a "Published Articles Database" using SQL server and ASP scripting
- Design front-end of the database using an Html editor
- Test the software using published articles provided by BESC secretary
- Publish the database on Al-Biruni development server (BESC)
- Create an end of project report
- Create an end of project MS PowerPoint presentation

Evidence Based Decision Support

Head

Bushra Siddiqui

Members

Mohamed Shoukri, PhD
Shazia Naz Subhani, MSc
Abdelmuniem Eldali, MSc
Wilhelmina Ventura
Mansoor Baig

The group serves as a core unit that provides higher administration and Research Center policy makers with needed expertise to facilitate the design of tools needed to advance knowledge and promote innovations by using advanced healthcare information technology and evidence-based methodologies.

Our mission is to instigate trans-disciplinary work related to how social factors, financing systems, organizational structures and processes, health technologies, and personal behaviors affect access to healthcare, the quality and cost of healthcare, and ultimately our health and well-being.

Our objectives include:

- To undertake multi-disciplinary work related to health systems and health care delivery.
- Promote a vibrant research culture for quality improvement in KFSH & RC by enhancing and facilitating interaction between investigators in different disciplines
- Improve and promote efficiency and effectiveness in health care delivery
- Investigate how organization and financing influence the quality and accessibility of care
- Support evidence-based policymaking
- Develop and maintain decision support systems that will facilitate health care research in KFSH & RC

RESEARCH PROJECTS

Project title

Data Analysis and Projection of the Congenital Heart Defects Registry Data

Project description

The inception of the Congenital Heart Defects Registry (CHDR) in 1998 started in King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia as a humble effort to answer the many questions related to the incidence and prevalence of Congenital Cardiac Defects in the Saudi population. A total of 16,871 patients from King Faisal Specialist Hospital and Prince Sultan Cardiac Center are registered and entered into the registry database. With such a rich volume of data, our group has provided the registry with a new online data analytics and visualization service making use of the SuperStar Suite platform. The interpretation and projection of data in the form of real-time, interactive charts and reports, with the help of our Dynamic Health Statistics Platform, will be used in providing better service to the patients, as well as helping our governmental health care providers and policy-makers in their future healthcare planning.

Project title

Data Analysis and Projection of the National Diabetes Registry Data

Project description

The National Diabetes Registry is a collaborative project between King Saud University Hospital and King Faisal Specialist Hospital & Research Center (KFSH&RC), Riyadh. Currently the registry is registering patients from 30 different hospitals from Riyadh region. This is a pioneering registry in its field. The purpose of this registry is to be a reliable, valid, and timely information source for Diabetes in the Kingdom of Saudi Arabia (KSA). The registry aims to identify risk factors related to Diabetes and to provide statistics to public health programs and health care professionals for use in planning and evaluation. With such a rich volume of data, our group has provided the registry with a new online data analytics and visualization service making use of the SuperStar Suite platform. The interpretation and projection of data in the form of real-time, interactive charts and reports, with the help of our Dynamic Health Statistics Platform, will be used in providing better service to the patients, as well as helping our governmental health care providers and policy-makers in their future healthcare planning.

Project title

Data Analysis and Projection of the Cleft Lip/Palate Registry Data

Project description

Cleft Lip/Palate & Craniofacial anomalies cause long-term morbidity, mortality and contribute substantially to long-term disability in children as well as tremendous emotional and financial stresses for affected families and individuals. With this in mind, Cleft Lip/Palate and Craniofacial anomalies registry is submitted with a mission "To promote better understanding of the CLCP/Craniofacial anomalies and to improve patient care and health care planning in the Kingdom of Saudi Arabia." The registry is a coordinated collaboration between the department of Dentistry and department of Biostatistics, Epidemiology and Scientific Computing (BESC). With such a rich volume of data, our group has provided the registry with a new online data analytics and visualization service making use of the SuperStar Suite platform. The interpretation and projection of data in the form of real-time, interactive charts and reports, with the help of our Dynamic Health Statistics platform, will be used in providing better service to the patients, as well as helping our governmental health care providers and policy-makers in their future healthcare planning.

Project title

Data Analysis and Projection of the National Epilepsy Registry Data

Project description

This Epilepsy Registry, established in 2003, is a first of its kind in the Kingdom of Saudi Arabia. It serves as a resource to improve the understanding of epilepsy and to assess the magnitude and impact of this disorder on the society. Currently, the registry has registered almost 4000 patients and is under continuous maintenance and support. With such a rich volume of data, our group has provided the registry with a new online data analytics and visualization service making use of the SuperStar Suite platform. The interpretation and projection of data in the form of real-time, interactive charts and reports, with the help of our Dynamic Health Statistics platform, will be used

in providing better service to the patients, as well as helping our governmental health care providers and policy-makers in their future healthcare planning.

Project title

ITA Employee Satisfaction Survey Analysis

Clients: Department of Organization and Management

Project description

The Employee satisfaction survey was conducted on a departmental level to analyze and present the findings that were meant to capture employee responses to questions categorized thematically according to a set of given analysis criteria. The responses were classified according to gender, nationality, position and class. A detailed analysis to the responses, as well as an in depth look at the different levels of interpretation, was performed and the results were shared on the SuperStar Suite platform. Following data projection, suggestions to actions and recommendations for consideration were given to help with the course of action.

Project title

Medical Insurance Survey Analysis

Clients: Department of Quality Resource Management

Project description

The Medical Insurance Survey was conducted on a hospital level to analyze and present the findings that were meant to capture employee responses to questions related to third party medical insurance possibilities as opposed to King Faisal Hospital's medical plan. A detailed analysis to the responses, as well as an in depth look at the different levels of interpretation, was performed and the results were shared on the SuperStar Suite platform for the decision-makers to base their actions on.

Project title

Medical Second Opinion Data Analysis

Clients: Department of Health Outreach Services

Project description

The Medical Second Opinion Database Application allows the coordinator of a medical second opinion to register detailed information about a complete second opinion procedure. The application captures variables that are useful in making strategic decisions about the amount of resources spent as well as the cost-effectiveness in making a second opinion. The data captured in the database is projected using the SuperStar Suite platform and is aimed at helping the management make evidence-based decisions using the facts presented in the reports and charts.

Project title

Data Validation and Electronic Sample Size Calculation

Clients: Department of Quality Management

Project description

Data validation is an important tool for understanding the quality of data and for establishing the level of confidence decision makers can have in the data. Data validation becomes one of the steps in the process of setting priorities for measurement, selecting what is to be measured (clinical or managerial), selecting and testing the measure, collecting the data, validating the data, and using the data for improvement. To support the establishment of an Administrative Policy and Procedure for validation and publication of data, our group was involved in providing the Quality Resource Management Department with expert opinion that helped outline the process of validating data collection across the organization as well as publishing or posting data outside the organization. Moreover, an Electronic Sample Size Calculation method was developed in-house to facilitate the computation of a statistically valid sample size based on a given population size N.

UPCOMING PROJECTS

Project title

Data Analysis and Projection of the Breast Cancer Registry Data

Project description

The mission of the Saudi Breast Cancer Research Program (SBCRP) is to eliminate breast cancer by leading innovation in research, communication, and collaboration in the Saudi scientific and lay communities. The registry is a coordinated collaboration between the Breast Cancer Center and department of Biostatistics, Epidemiology and Scientific Computing (BESC). The registry aims at registering patients with breast cancer in an effort to find treatments, preventions and cures. With such a rich volume of data, our group will provide the registry with a new online data analytics and visualization service making use of the SuperStar Suite platform. The interpretation and projection of data in the form

of real-time, interactive charts and reports, with the help of our Dynamic Health Statistics platform, will be used in providing better service to the patients, as well as helping our governmental health care providers and policy-makers in their future healthcare planning.

Project title

Data Analysis and Projection of the Tumor Registry Data

Project description

The Tumor registry database includes over 70,000 cases and reports to the Saudi Cancer Registry. In collaboration with the Oncology Center, our group will perform a data projection of the cancer incidence, treatment, trends and outcomes to fully allow the researcher and the public to understand how the cancer is progressing in the country and its regions. With the new online data analytics and visualization service making use of the SuperStar Suite platform, the interpretation and projection of data in the form of real-time, interactive charts and reports, will be used in providing better service to the patients, as well as helping our governmental health care providers and policy-makers in their future healthcare planning.

Project title

Balanced Score Card Indicator Analysis

Clients: Office of the Chief Executive Officer (CEO)

Project description

The balanced score card has evolved from its early use as a simple performance measurement framework to a full strategic planning and management system. It enables organizations to clarify their vision and strategy and translate them into action. It helps planners identify what should be done and measured. Our group will design a data projection of scorecards in the areas of Research and Development that will include Publications (Scientific paper publications, abstracts, technical reports); Number of trainees handled by the Research Center; Number of Seminars, workshops, conferences and professional meetings held; and the number of grants employed in the Research Center. The projection, using the SuperStar Suite platform, will enable the policy makers and the higher executive management in making strategic decisions about the amount of research and activities carried out in the Research Center.

Project title

Electronic Evaluation Process for Trainees and Teachers

Clients: Department of Academic and Training Affairs

Project description

The Postgraduate Education Committee at Academic and Training Affairs is embarking on changing the paper-based evaluation process of trainees to electronic/online and paperless process. Our group is involved in designing this application for them, as well as projecting the outcomes on the SuperStar Suite platform. The success of this project could be stimulating for the Saudi Commission for Health Specialties to adopt it in lieu of its current paper-based unidirectional evaluation process.

THE

Centre for Clinical Studies and Empirical Ethics

The Centre for Clinical Studies and Empirical Ethics

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)
Hala Amer, MD (Grant Funded Employee)
Ma. Victoria G. Ventura
Mohamed Samman, PhD (Joined CCSEE on 12 June 2010)
Nada Bin Hashim, RN (On unpaid leave from 20 March 2010 – Dec 2011)
Rajaa Hussein, RPh
Reem Al-Swayeh, RPh
Saleh Al-Dgither
Saleh Fahad Al Othman, MD, PhD (Joined CCSEE on 12 June 2010)
Syed N. Alvi, PhD
Weam Al-Jasim, RPh (until 19 April 2010)
Basma Fayad (Trainee from 9 Oct 2010 – 19 Jan 2011)
Abdullah Talat Eissa (Trainee from 9 Oct 2010 – 4 Feb 2011)

The Centre for Clinical Studies and Empirical Ethics (CCSEE) has established itself as a national/regional centre for conducting bioequivalence, clinical, and empirical ethics studies; and for training clinical/laboratory research professionals. The activities of the CCSEE are strategically chosen to: 1) build an appropriate, self-sustaining infrastructure, and 2) concentrate on projects of direct translational values. The Bioanalytical Laboratory of the CCSEE has been accredited by the College of American Pathologists (CAP) since May 2007. The gross income (fee from service) for the year 2010 was SR 126,000.00.

DRUG ASSAY DEVELOPMENT AND VALIDATION

No.	Drug Name	Analysis Method	Volume (ml)	Matrix	Range (mg/ml)
1.	Ceftriaxone	HPLC-UV	0.25	Plasma	0.2-200
2.	Glipizide	HPLC-UV	1.00	Plasma	0.015-2.0
3.	Bisphenol A (BPA)	HPLC-FL	1.00	Water	0.05-20*
4.	25 Hydroxy Vitamin D2	HPLC-UV	1.00	Plasma	2.5-100*
5.	25 Hydroxy Vitamin D3	HPLC-UV	1.00	Plasma	2.5-100*
6.	BPA Diglycidyl Ether	HPLC-FL	1.00	Water	0.03-30*
7.	Paracetamol	HPLC-UV	0.50	Plasma	0.5-40
8.	Vitamin D2	HPLC-UV	20	Milk	2.5-60*
9.	Vitamin D3	HPLC-UV	20	Milk	2.5-60*
10.	Testosterone	LCMS-MS	1.0	Saliva	20-400**

CLINICAL

Project title

Does Vitamin D improve glycemic control in type II DM? A double-blind randomized controlled trial. RAC# 2101039

Abstract

Both vitamin D deficiency/insufficiency and type II DM/ prediabetes are highly prevalent in Saudi Arabia. Vitamin D status has been negatively associated with the presence of type II DM and glycemic control. A cause-effect relationship between vitamin D deficiency and glycemic control has not been established.

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

300 adult, type II diabetics with stable HA1c between 6.5 and 8% and total 25 OH vitamin D level between 10-30 nmol/L will be stratified according to their body mass index: ≤ 25, ›25 to ≤ 30, ›30 to ≤ 40 kg/m2 then randomized to receive 2000 or 5000 IU of vitamin D3 or a placebo for six months. Diabetes management will not be otherwise changed. Patients who become hypercalcemic or hypercalciuric or develop a HA1c above 8.5% or clinically unacceptable hypoglycemic episodes will be withdrawn from the protocol but will continue to be followed up.

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

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

Status/Progress:

External funding by the National Plan for Science, Technology and Innovation (NPSTI), approved.

Project title

Does Vitamin D reduce risk of developing type II DM in Prediabetes? A Double blind randomized controlled trials. RAC# 2101040

Abstract

Both vitamin D deficiency/insufficiency and type II DM/ prediabetes are highly prevalent in Saudi Arabia. Vitamin D status has been negatively associated with the presence of type II DM and glycemic control. A cause-effect relationship between vitamin D deficiency and the development of type II DM has not been established.

We plan to conduct a 2 year, double blind, randomized, placebo controlled trial on the effect of vitamin D3 supplement on the incidence of type II DM in high risk individuals.

500 otherwise healthy adults with impaired fasting glucose or/and impaired glucose tolerance and total 25 OH vitamin D level between 10-30 nmol/l will be stratified according to body mass index: ≤ 25, > 25 to ≤ 30, > 30 to ≤ 40 kg/m2 then randomized to receive 5000 IU of vitamin D3 or a matching placebo for 2 years. Individuals who become hypercalcemic or hypercalciuric or develop DM will be withdrawn from the protocol but will be followed up. The following measurements will be obtained at baseline and on monthly bases: height, weight, blood pressure, fasting glucose, fasting insulin, 2-hour post challenge glucose, 25 OH vitamin D3 and D2, and calcium blood levels, as well as urine calcium to creatinine ratio.

The primary endpoint is the development of DM as defined by fasting and/or 2-hour post challenge glucose levels. The incidence of DM is the primary analysis. Time to event analysis and slope of fasting and 2-hour post challenge glucose levels are the secondary analyses of the primary endpoint. Secondary endpoints include AUC of systolic and diastolic blood pressure, weight, and 25 OH vitamin D level; as well as fasting insulin to glucose ratio, and the incidence of hypercalcemia and hypercalciuria.The primary endpoint will be analyzed by 2-tail unpaired t test, log rank test, and Cox proportional hazards model.

The study will test the hypothesis that vitamin D deficiency and the development of type II DM are causally related and that vitamin D repletion can prevent type II DM. The contribution of improved insulin secretion vs action will be explored. The information obtained will be important for scientists in the field, managing physicians, and policy makers.

Status/Progress:

Submitted for external funding.

Project title

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

Abstract

Vitamin D deficiency is common in Saudi Arabia and world wide. 25 OH vitamin D level is the best indicator of vitamin D status. Vitamin D supplements are available as vitamin D2 or D3, in small daily or large weekly/monthly doses. Controversy continues on the relative potency of vitamin D2 compared to D3 and of daily compared to weekly or monthly doses, in increasing/maintaining total 25 OH vitamin D level.

We plan to conduct a blinded, randomized controlled trial to compare the effect of various vitamin D supplements on 25 OH vitamin D levels in healthy adults with starting 25 OH vitamin D level between 20 to 50 nmol/L.

We will randomize 800 individuals to one of eight groups: daily dose of 2000 IU D2, 2000 IU D3, or a combination of 1000 IU D2 and 1000 IU D3; 2-weekly doses of 25,000 IU D2 or 25,000 D3 IU; or 4-weekly doses of 50,000 IU D2 or 50,000 IU D3; or a placebo given daily. Treatment will continue for 5 months. The randomization sequence, stratified by body mass index (≤ 30, › 30 kg/m2) and gender (males and non-pregnant females) will be generated using an on line program. Participants as well as personnel involved in the determination of vitamin D/metabolites level and data analysis will be blinded as to the content of the individual participant's assignment. Using a locally validated reversed-phase HPLC method, vitamin D (total and fractionated) and 25 OH vitamin D (total and fractionated) will be measured at baseline, days 1,2,3,4,7,14, and biweekly thereafter. Serum Ca and phosphate levels, and urine Ca and phosphate to creatinine ratios will be obtained at baseline and at 5 months.

The primary endpoint is the area under the curve of days 1 to 140 (AUC) of total 25 OH vitamin D levels. The AUC of the placebo group will be used to determine changes in total 25 OH vitamin D levels that are not related to intervention. Secondary endpoints include Cmax and Tmax of 25 OH vitamin D, AUC of vitamin D, and the incidence of hypercalcemia and hypercalciuria.

The (adjusted) primary endpoint of the three daily regimens, the two 2-weekly regimens, the two 4-weekly regimens, the three vitamin D2 regimens, and the three vitamin D3 regimens will be compared by ANOVA (5 ANOVA tests). Pair-wise comparison will be conducted by unpaired 2-tail t test.

The study will establish the relative efficacy of the various oral supplements of vitamin D and whether vitamin D2 supplement adversely affect 25 OH vitamin D3 levels. The information obtained will be important for scientists in the field, managing physicians, and policy makers.

Status/Progress

External funding by the National Plan for Science, Technology and Innovation (NPSTI), approved.

Project title

Magnitude of Changes in 25 OH Vitamin D3 levels after Vitamin D3 supplementation. A prospective study. RAC# 2101042

Abstract

Vitamin D deficiency is common in Saudi Arabia and world wide. 25 OH vitamin D level is the best indicator of vitamin D status. The determination of the appropriate dose of vitamin D supplement is essential for management of vitamin D deficiency as well as for designing vitamin D fortification programs. The increments in 25 OH vitamin D levels following various doses of vitamin D supplement for different genders, body weights, and starting 25 OH vitamin D level have not been well defined. The time course of depletion of repleted vitamin D stores is also not known.

We plan to conduct a double blind randomized study on 32 cohorts to determine levels of 25 OH vitamin D following supplementation with different doses of vitamin D3 for 5 months and their withdrawal for 3 months.

1080 healthy volunteers stratified into 32 cohorts (33-34 subjects each) according to total 25 vitamin D level (≤20, › 20 to ≤ 30, › 30 to ≤ 50, › 50-100 nmol/l), body mass index (≤ 25, › 25 to ≤ 30, › 30 to ≤35, ›35 kg/m2), and gender (males and non-pregnant females). In each strata, 11 individuals will be randomized to one of three vitamin D3 daily supplement (1000, 3000, 5000 IU) for 5 months followed by a follow up without supplement for another 3 months. A cohort of 24 individuals will be randomly selected (one from each of the 24 groups with 25 OH vitamin D levels › 20 nmol/l) to serve as a placebo control. Using a locally validated reversed-phase HPLC method, vitamin D3 and 25 OH vitamin D3 will be measured at baseline, days 1,2,3,4,7,14, and biweekly thereafter. Serum calcium and phosphate levels, and urine calcium and phosphate to creatinine ratios will be obtained at baseline and bimonthly thereafter. All measurements will be performed at the CCSEE laboratory.

The primary endpoint is the slope of the dose (vitamin D3)-response (25 OH vitamin D3 level) curve for each cohort. The slope of the placebo group will be used to determine changes in 25 OH vitamin D3 levels that are not related to study intervention.

Secondary endpoints include the slope of the dose (vitamin D3)-response (vitamin D3 level), slope of decline in 25 OH vitamin D level after withholding supplement, and the incidence of hypercalcemia and hypercalciuria. The point estimate as well as the 95% confidence interval of the primary endpoint in each cohort will be determined. In addition, linear regression analysis will be performed.

The study will establish the optimal supplement dose for various demographic groups and the time course of depletion of vitamin D stores. The information obtained will be important for scientists in the field, managing physicians, and policy makers.

Status/Progress:

Submitted for external funding.

Project title

Hyponatremia in Thyroid Cancer. RAC# 2101050

Abstract

Patients with differentiated thyroid cancer are instructed to withhold thyroid hormone treatment, follow a low salt (iodine) diet, and increase fluid intake, in preparation for/shortly after radioactive iodine (RAI) therapy. Such instructions in combination with potential nausea caused by RAI, and anxiety may result in serious iatrogenic hyponatremia in patients who are in isolation.

We plan to study the incidence and severity of hyponatremia in a cohort of 220 thyroid cancer patients around the time they are cleared for discharge after RAI therapy. Discharge sodium level will also be correlated with pre RAI dosing sodium level, TSH level, age, and estimated fluid intake; and compared between males and females and among patients with relevant co-morbidities (such as DM). The study will be conducted according to the Declaration of Helsinki and RAC regulations. A written consent will be obtained. The sample size is based on an expected incidence of hyponatremia of 5% to 10% (with a desired precision of ± 3% and 4%, respectively). The confidence interval on the point estimate of the incidence of both mild hyponatermia and moderate to severe hyponatremia will be determined. Correlations will be analyzed using Pearson r test. Subgroups will be compared using unpaired t test (mean Na level) and chi square test (frequency of hyponatremia). Discharge and pre-dosing sodium levels will be analyzed by paired t test.

The study is expected to provide important information relevant to the management of thyroid cancer patients undergoing RAI therapy.

Status/Progress:

In progress.

Project title

Vitamin D Content in Fortified liquid milk in Saudi Arabia. RAC# 2100014

Abstract

A reliable high performance liquid chromatography (HPLC) assay for simultaneous determination of vitamin D2 (VD-2) and vitamin D3 (VD-3) levels using indeno (1,2,3-CD) pyrene as an internal standard (IS) was developed. The samples were saponified over night at room temperature with a mixture of ethanol and potassium hydroxide (KOH). The digest was extracted with hexanes and washed with 5% ethanol in KOH. After evaporation, the residue was dissolved in acidic methanol and centrifuged. 100 µl of the clear solution was injected; and separation was achieved on Zorbax C18 column. The mobile phase, consists of methanol, acetonitrile and water that was used in a gradient elution mode. The eluents were monitored by photodiode array detector, with the wavelength set at 265 nm. No interference with endogenous components was observed. The relationship between the concentration of VD-2 and VD-3 in milk and peak area ratio (VD-2 and VD-3) to the IS was linear over the range of 100 - 2400 IU/L. Mean extraction recoveries of VD-2 and VD-3 from milk samples were over 90%, and 62% for IS. The stability of VD-2 and VD-3 in milk was determined under various storage conditions. The method was applied in assessing the levels VD-2 and VD-3 in milk commercially available in the market of Riyadh, Saudi Arabia.

Status/Progress

In progress.

Project title

Interaction Between Drug and Placebo Effect: Randomized Placebo-Controlled Trials may not be accurate in determining Drug Effect Size. RAC# 2111 001

Abstract

Background: The total effect of a medication is the sum of its drug effect, placebo effect (meaning response of placebo), and their possible interaction. Current interpretation of the results of clinical trials (the gold standard in evidence based medicine) assumes no such interaction. Using a novel cross-over balanced placebo design and caffeine as a model drug (KACST ARP-26-45), we have recently shown that a negative interaction does exist; suggesting that the size of drug effect as currently measured by clinical trials may not be accurate. Due to the novelty of the findings and their important clinical practice and research implications, they need to be confirmed using another drug; and the size of drug effect measured using the novel design need to be directly compared to that measured using conventional clinical trial design.

Design: A cross-over balanced placebo plus randomized placebo-controlled clinical trial design.

Methods: 480 adults will be double-blindly randomized to three groups: first generation H-1 receptor antagonist-hydroxyzine (25 mg), placebo, or hydroxyzine+placebo group. The first two groups will receive the assigned intervention described by the investigators as hydroxyzine or placebo, in a randomized crossover design. The third group will receive hydroxyzine and placebo in a randomized double-blind placebo-controled crossover design. Group assignment will be concealed from volunteers and recruiters. Data collectors will be blinded to group assignment and intervention assignment. Volunteers will be partially deceived to the intervention assignment in the first two groups and blinded in the third group. The interventions to the third group will be also administered blindly. Serum hydroxyzine levels will be determined 3 hours post intervention from all volunteers to verify compliance and help maintain deception/blinding. Seven-hour-area-under-the-curve of drowsiness and dryness of the mouth (on 100 mm visual analog scales) as well as mean percent of time of reporting these symptoms on a dichotomous scale will also be determined. Using ANCOVA (the model includes sequence, subjects nested within sequence, period, and intervention as appropriate, as well as baseline value as a covariate), drug, placebo, placebo-plus-interaction, and total effects will be estimated by comparing outcomes (in the first two groups) after receiving hydroxyzine described as placebo to receiving placebo described as placebo, receiving placebo described as hydroxyzine or placebo, receiving hydroxyzine described as hydroxyzine or placebo, and receiving hydroxyzine described as hydroxyzine to receiving placebo described as placebo, respectively. Drug effect will be also conventionally determined using data from the third group. The placebo effect will be compared to the placebo+interaction effect and the conventionally measured hydroxyzine drug effect will be compared to the novely measured hydroxyzine drug effect, using independent 2-tail t test.

Utility: The results of the study are expected to further our understanding of a widely used medical intervention, i.e.,

placebo, and help assess the appropriateness of randomized clinical trials in determining the size of drug effect.

Status/Progress:

Submitted for external funding.

Project title

The placebo effect may involve modulating drug bioavailability. RAC# 2101 105

Abstract

Background: The total effect of a medication is the sum of its drug effect, placebo effect (meaning response of placebo), and their interaction. Current interpretation of clinical trials (the gold standard of evidence-based-medicine) assumes no interaction, and the mechanism(s) underlying such interaction have not been fully explored. One possibility is that the placebo effect may modulate drug bioavailability. Using caffeine as a model drug (KACST ARP-26-45), we have recently shown that the placebo effect of caffeine ingestion prolongs caffeine half life. Due to the novelty of this finding and its important clinical practice and clinical practice and clinical research implications, it needs to be confirmed in another set of subjects and extended to additional drugs.

Design: Balanced cross-over, single-dose, two-period, two-group deign comparing caffeine, paracetamol, cephalexin, and ibuprofen described as such (overt) to the same medication described as placebo (covert).

Methods: 32, 50, 50 and 30 healthy adult volunteers will be enrolled in the caffeine (300 mg), paracetamol (500 mg), cephalexin (500 mg), and ibuprofen (400 mg) cross-over studies, respectively. Volunteers will be partially deceived to the intervention assignment (i.e., in the covert arm). Serum levels of each drug will be blindly determined by locally validated HPLC assays. Plasma half life (primary outcome) as well as Cmax, Tmax, and AUC (secondary outcomes) of each drug will be determined and analyzed by ANOVA. The model will include group, subjects nested within group, period, and intervention (overt vs. covert drug). In a secondary analysis, the difference between covert and overt drug in the means of the long-transformed values of the pharmacokinetics end points will be analyzed by 90% confidence interval.

Utility: The results of the study are expected to further our understanding of the mechanism of action of a widely used medical intervention, i.e., placebo. The results will be important for both clinical practice and clinical research.

Status/Progress:

Submitted for external funding.

Project title

Salivary Testosterone Level in Healthy Male Arabs. RAC# 2071 081

Abstract

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 validated, recruiting.

Project title

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

Project description

Generic formulations of prescription drugs can, through their relatively lower cost, improve healthcare as long as they maintain their registration-quality and public trust. On the other

hand, the market availability of several generic formulations raises a concern regarding their interchangeability, despite being proven to be individually therapeutically interchangeable with their corresponding innovator formulation.

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

The 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:

Funded by the Long-Term Comprehensive National Plan for Science, Technology and Innovation (NPSTI), recruiting.

EMPIRICAL ETHICS

Project title

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

Project description

There is a huge gap between organ supply and demand worldwide. Despite being the predominant source, cadaveric organ donation is limited, mainly because of failure to obtain consent. The consenting process currently used in Saudi Arabia is explicit consent. Other types of consenting that may improve organ procurement are potentially available. We aim to study the opinions and preferences of the Saudi public in regards to several types of consenting. 1000 Saudi adults (including patients and their companions) at the outpatient clinics of KFSH&RC will be approached to complete self- or investigator-administered questionnaire. Pertinent demographic data will be collected and correlated with responses. This study is expected to provide ethicists and policy makers with important information on acceptable ways to improve the consenting rate for organ donation. It will also help formulate a Saudi public view and thus contribute to the global bioethics view on organ donation.

Status/Progress

Writing manuscript.

Project title

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

Project description

The informed consent (IC) is an established ethical and legal requirement for providing medical care. IC can be general or specific, implicit or explicit, and written or verbal, depending mainly on the intervention provided. The "function" of IC and the type and extent of information to be provided continue to be controversial. As part of our empirical ethics program, we plan to explore the perception of KFSH&RC's adult patients about the current and desired function of procedure-specific, explicit, written informed consent. We will also explore their perception of the current (and desired) type and extent of information provided. 650 individuals representing KFSH&RC adult patients who had, or are going to have, surgery or a medical procedure will be recruited in the outpatient setting. An eight-page questionnaire developed by the investigators will be self-or investigator-administered in Arabic. The questionnaire will be pre-tested on 20 patients. The response rate will be determined and data will be tabulated and related to type of procedure and patient's age, gender, health status, occupation, and level of education. The results of the study are expected to provide an empirical evidence of patients' perceptions and expectations of the IC that will help physicians/policy makers in educating patients, improving patient's satisfaction, and obtaining a "true" IC.

Status/Progress

Writing manuscript.

Project title

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

Project description

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

Status/Progress

Writing manuscript.

Project title

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

Project description

Human care at end-of-life (EOL) depends to a large extent on helping patients die the way they prefer. Patients have different EOL priorities which they hold at different hierarchy. These priorities are often not made known to either the family or the physicians, undermining surrogate decision making. Using the Q methodology, we plan to discover patterns of EOL priorities in Saudis. We will also compare these patterns between family members and between medical professionals and non-medical professionals. A Q set of potential EOL priorities that has been developed by the investigators will be piloted on 10 Saudi medical professionals and 10 Saudi non-medical professionals, for clarity, redundancy, inclusivity,

balance, and reproducibility. One hundred Saudi adult pairs (husband-wife, parents-children) will be asked to sort the Q set twice, first according to their own priorities and second according to what they think the priorities of their pairs are. In addition, 100 Saudi medical professionals will be asked to sort the Q set twice according to their own priorities and according to what they think the average Saudi patients' priorities are. The study is expected to provide physicians and policy makers with vital information on EOL priorities of Saudis. It will identify Saudi view(s) and contribute to global bioethics on EOL as well.

Status/Progress

Recruiting.

Project title

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

Project description

Background: Compliance with the International Committee of Medical Journal Editors (ICMJE) guidelines, which oblige journal editors not to accept publications that do not document conformation to ethical standards, has been variably inadequate world wide. Aim: To evaluate documentation of ethical conduct of human subject research studies published in Saudi medical journals and explore factors associated with such documentation.

Methods: A structured data collection tool was used to record documentation of the ethical guidelines that where followed, obtaining Institutional Review Board (IRB) approval, and obtaining informed consent for research and publication, in human subject research studies published between 1979 and 2007 in 11 accessible Saudi medical journals. Identified studies were classified as retrospective (medical records or biological samples-based), prospective non-interventional (medical records or biological samples-based), interventional, survey, or interview. Requirements for IRB review and/or informed consent were judged by the authors according to the US Office of Human Research Protection guidelines. The frequency (%) of studies that documented fulfilling the ethical requirements as well as the association between documentation rate and study type, year of publication, and country where research was conducted, were determined.

Results: 1838 human subject research studies were identified; 673 (36.6%) were retrospective, 480 (26.2%) prospective non-interventional, 341 (18.6) interventional, 279 (15.2%) survey, and 65 (3.5%) interview studies. Sixteen (0.9%) out of 1838 studies documented the ethical guidelines that were followed, with a higher documentation rate (P=0.003) for studies published after year 2000 (1.7%). Seventy one (8.6%) out of 821 studies requiring obtaining both IRB approval and informed consent, documented fulfilling both requirements, with a higher documentation rate (P<0.0001) for interventional studies (19.4%), studies published after year 2000 (19.7%), and studies performed outside Saudi Arabia (15.9%). Twenty three (2.3%) out of 1017 studies requiring IRB approval (but not informed consent) documented fulfilling this requirement, with a higher documentation rate (P<0.0001) for studies published after year 2000 (4.2%). None of the 9 articles containing identifying private information documented that consent to publish was obtained. Conclusion: The documentation rate of ethical conduct in human subject research studies published in accessible Saudi medical journals was low, suggesting ignorance of the (importance) of the ICMJE guidelines, especially for studies conducted in Saudi Arabia. The lower documentation rate for non-interventional studies suggests unawareness of the scope of human subject research, whereas the higher documentation rate after year 2000 suggests an on-going improvement.

Status/Progress

Manuscript submitted for publication.

Project title

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

Project description

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

non-malificence, and justice) will be examined. The association of various demographic factors with the identified models and the effect of formal ethical education will be studies. We will also explore the stability of the identified models/points of equilibrium over time, within demographic groups, and across topics. The results are expected to have important contributions to empirical studies of ethical resolution and to evidence-based ethics regarding current bioethical issues. It may show that beliefs aside, ethical resolution models/points of equilibrium may 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. 12th Semiannual Clinical Research Professionals' Course, 15-26 May 2010 (67.25 CME hours with commendation by the AACME).
2. 5th Semiannual LC&LCMS: Concept and Hands-On Training. Course, 6-10 June 2010 (17 CME credit hours by the SCHS)
3. 6th Semiannual LC&LCMS: Concept and Hands-On Training Course, 25-29 December 2010 (17 credit hours by the SCHS).
4. HPLC & LCMS: Basic unit operation training given to Basma Fayad from 9 October 2010 until 19 January 2011.
5. Clinical Research Coordinator Training given to Abdullah Talat Eissat from 9 October 2010 until 4 February 2011.

PUBLICATIONS

- A R Hussein, M Ahmed, S O Ahmed, P Manogran, Syed N Alvi, L C Platanias, KS Al Kuraya, Shabuddin. Thymoquinone suppresses growth and induces apotosis via generation of reactive oxygen species in primary effusion lymphoma. *Free Radical Biology and Medicine*. (Accepted).

PRESENTATIONS

- A validated reversed phase HPLC assay for the determination of Hydrochlorothiazide in human plasma. Syed N. Alvi, Muhammad M Hammami. Presented in the conference on Analytical Research Forum 2010, Loughborough University, United Kingdom, 26-28 July 2010.

Drug Analysis

1. Rajaa Hussein and Muhammad Hammami. Rabeprazole analysis in human plasma by fully validated HPLC assay. *Analytical chemistry*. 2010;9(3).
2. Reem Saleh AlSwayeh and Muhammad Hammami. Atorvastatin analysis by fully validated HPLC assay in human plasma. *Analytical Chemistry*. 2010;9(3).
3. Ahmed Yusuf and Muhammad Hammami. Validation of a new HPLC assay for glibenclamide in human plasma. *FABAD J Pharmaceutical Sciences*. In Press 2010.
4. Rajaa Hussein and Muhammad Hammami. Ceftriaxone stability and sensitive analysis by fully validated iron-paring HPLC assay in human plasma. 2010;9(4).
5. Reem Saleh AlSwayeh, Syed N Alvi, and Muhammad Hammami. Ampicillin analysis by fully validated HPLC assay in human plasma. *Analytical Chemistry*. In press 2010.
6. Al-Dgither S, Yusuf A, Hammami MM. Fluconazole: stability and analysis in human plasma by simple high performance liquid chromatography. *FABADJ Pharmaceutical Sciences*. In press 2010.
7. Syed N. Alvi and Muhammad M Hammami. Validated HPLC method for determination of caffeine level in human plasma using synthetic plasma: Application to Bioavailability Studies. *Journal of Chromatographic Science*. 2011, 49.
8. Rajaa Hussein andMuhammad Hammami. Determination of Ketoprofen level by fully validated HPLC assay. *International J of Pharmacy & Technology* (IJPT) (eISSN:0975-766X; CODEN:IJPTFI) Volume-3 Issue-1 Jan-March 2011.

Empirical Ethics

1. Mohammad Qadri, Muhammad M Hammami, Hunaida ABDU and Eman AlGaai. Saudi Views on Consenting Research on Medicla Records and Leftover Tissue Samples. BMC Medical Ethics 2010, 11:18doi:10.1186/1472-6939-11-18.
2. Muhammad M Hammami, Sahar Attalah, and Mohammad Alqadery. Which medical error to disclose to patients and by whom? Public preference and perceptions of norm and current practice. *BMC Medical Ethics* 2010, 11:17doi:10.1186/1472-6939-11-17.

3. Hunida E Abdulhameed, Muhammad M Hammami, and Elbushra A Hameed Mohamed. Disclosure of terminal illness to patients and families: Governing codes in Islamic and Arabic countries. Submitted to *J Medical Ethics*. In press 2011.

Study designs/placebo

1. Muhammad M Hammami, Eman A Al-Gaai, and Syed N Alvi. Interaction between drug and placebo effects: a crossover balanced placebo design trial. *Trials 2010*, 11:110 (19 November 2010).

THE DEPARTMENT OF

Genetics

The Department of Genetics

Chairman
Brian Meyer, PhD

Administrative Support Staff
Lilia Fernandez
Klea M. Edquiban
Ralyn Alma O. Castillo
Maritess Santiago
Emalyn Samonte

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

Behavioral Genetics

Head
Nada Al Tassan, PhD

Members
Dania Khalil, BSc
Jameela Shinwari, MSc
Manar Ghanam, BSc

The main objective of the unit is to explore the molecular basis of different monogenic and oligogeneic disorders mainly focusing on multiplex families where a specific trait segregates. We use the latest technology in order to gain insight in to the genetics of these disorders and eventually understand the function of the genes and the role of the proteins in the biological system. Identifying the underlying genetic causes of such disorders will help in improving clinical diagnosis, genetic testing and counseling for affected individuals and families in Saudi Arabia. In addition the unit provides diagnostic and research services to characterize mutations in different simple and complex diseases.

RESEARCH PROJECTS

Project title

Molecular Analysis of APTX and SETX genes in Saudi Families with Ataxia Ocular Apraxia (AOA) (RAC # 2050036).

Investigators: Al-Tassan N, Bohlega S, Imtiaz F, Yamani S.

Project description

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

Progress

Five families with AOA type I (family B,C,D)or II (family A and D) were enrolled in the study (2 or more affected individuals). Comprehensive screening for the whole open reading frame (ORF) of the related genes was performed and completed in all families. A novel truncating mutation (c.6859 C>T, R2287X) in exon 20 of the SETX gene was identified as the disease causing mutation in family A. The MRE11 common reported mutation W210C was idetnfied in two unrelated families with AOA1. A new locus on chromosome 17p12-p13 (Ensembl cytogenetic band) with a LOD score of 3.38 was identified in a family with 4 affected individuals with AOA2, candidate genes are being screened in immediate and extended family members.

Project title

Genetic Mutations in Weill Marchesani Syndrome (WMS) in Saudi Arabia (2070008)

Investigators: Al-Tassan N, Morales J, Bakheet D, Al-Mahrouqi R.

Project description

The aim of the study is to identify families with WMS which is a rare connective tissue disorder associated with lens abnormalities, and screen for mutations in the common known genes (ADAMTS-10, FBN-1).

Progress

Sequencing of the whole coding region of the related genes (ADAMTS-10, FBN1) is being performed in affected individuals from families with WMS phenotype. Three novel missense mutations in ADAMTS10 were identified in three families. In addition to the three mutations identified in ADAMTS17 the gene mapped by this group in 2009, two additional novel mutations were identified in new recruited cases. Further analysis and characterization of these genes in more patients is ongoing.

Project title

Genetic evaluation of congenital eyelid and eye movement abnormalities. (2080020)

Investigators: Khan A, Al-Tassan N.

Project description

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

Progress

Comprehensive screening for the whole open reading frame (ORF) of KIF21Awas 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 in KIF12A was identified in two siblings with CFEOM2. Sixty other patients have been enrolled in the study and mutational screenings have revealed several novel and reported polymorphisms in some of these genes and novel ROBO3 missense mutation P771L was identified in a patient with synergistic convergence. A splice mutation in FRMD7 in siblings with x-linked nestagmous was also identified. Twenty two families (2 or more affected) are being analyzed using 10-250K micro-array chips to identify possible new disease causing loci. Sib-pair and linkage analysis is ongoing.

Project title

Characterizing Genetic Abnormalities in Autistic Spectrum Disorder (ASD) patients in Saudi Arabia. (RAC # 2080020)

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

Project description

This multidisciplinary multicentre study aims to investigate the genetic basis of ASD patients in Saudi Arabia using genome-wide linkage analysis of ASD families with 3 or more affected

individuals using microarray based genotyping. Simplex cases (100) will also be studied using a homozygosity based approach to identify underlying genes.

Progress

Forty nine 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 3 shared disease loci on chromosomes 3p11,4q11-q12,14q23.3-q24.1. Genes in these regions are being further investigated.

Project title

Genetic characterization of hemoglobinopathies in Saudi Arabia (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

110 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). (2020 007).

Investigators: Bakheet D, Tassan N and Bin Abbas Bassam.

Project description

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

Progress

15 patients were enrolled from KKSH&RC Screening for both genes identified a number of novel and reported variants. Deletions were also identified in some patients.

Project title

The Molecular Basis of Inherited Reproductive Disorders (RAC# 2091054)

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

Project description

This approved study in collaboration with Reproductive Endocrine Unit, Massachusetts General Hospital, Boston, USA, aims to identify genes that control puberty and reproduction in humans and characterize the phenotypic spectrum of patients with these genetics defects. 700 patients were screened for 16 genes involved, a number of novel and previously reported mutations were identified.

FUTURE RESEARCH DIRECTION

The main future goal is to establish a research facility that utilizes the latest molecular analysis techniques to study genetically diverse complex disorders to identify new disease causing genes and novel mutations and to study the functional role of these mutations.

PUBLICATIONS AND POSTERS

- Khan, A.O., Shinwari, J, Abu Dhaim N., Khalil D., Al Sharif L., Al Tassan N. (2011). Potential linkage of different phenotypic forms of childhood strabismus to a recessive susceptibility locus 16p13.12-p12.3). *MolVis* 17:971-6.
- Khan, A.O., Shinwari, J., Omar, A., Khalil, D., Al-Anazi, M., Al-Amri, A., and Al-Tassan, N.A. (2011). The Optic Nerve Head in Congenital Fibrosis of the Extraocular Muscles. *Ophthalmic Genet.* (March 2011, published online)
- Khan, A.O., Shinwari, J., Omar, A., Al-Sharif, L., Khalil, D.S., Alanazi, M., Al-Amri, A., and Al Tassan, N. (2011). Lack of KIF21A mutations in congenital fibrosis of the extraocular muscles type I patients from consanguineous Saudi Arabian families. *Mol Vis* 17:218-224.
- Bohlega, S.A., Shinwari, J.M., Al Sharif, L.J., Khalil, D.S., Alkhairallah, T.S., and Al Tassan, N.A. (2011). Clinical and Molecular Characterization of Ataxia with Oculomotor Apraxia Patients In Saudi Arabia. *BMC Med Genet* 12:27.

- Al-Qasem, A., Toulimat M.,. Eldali A., Tulbah A., Al-Yousef N., Al-Daihan S., AlTassan N., Al-Tweigeri T., Aboussekhra A. (2011). TP53 genetic alterations in Arab breast cancer patients: Novel mutations, pattern and distribution. *Oncology Letters* 363-396 (published online)
- Khan, A.O., Shinwari, J., Al-Sharif, L., Khalil, D., and AL Tassan, N., (2011). Optokinetic drum testing reveals prolonged pursuit in asymptomatic female carriers of a novel FRMD7 splice mutation (c.1050+5 G>A). *Archives of Ophthalmology* (In Press)
- AL Tassan, Shinwari J, Al Sharif L, Khalil D,.Almuslamani A, Khalak H, Ghannam M, Meyer B, Nester M, Aldosari M. Copy Number Variation and Loss of Heterozygosity In Saudi Patients With ASD. 60th annual meeting of the American Society of Human Genetics, Washington, USA 2-6 Nov 2010 (Poster).
- Characterization of Genetic Abnormalities in Saudi Autistic Children. Autism Workshop, Doha, Qatar 30th April-1st May 2011 (Presentation).
- Shinwari J,Adi A, Aldosari M, Khalil. D, Abu-Doheim N,, Almuslamani A,Nester M, Ghannam M, Meyer BF and Al Tassan N.Loss of Heterozygosity Analysis in Saudi Patients with ASD . IMFAR 2011, USA May 2011 (Poster).

Cardiovascular and Pharmacogenomics Unit

Head
Dr. Nduna Dzimiri

The Cardiovascular and Pharmacogenomics Unit currently focuses on endeavouring to understand the role of gene polymorphism(s) (SNPs) in the manifestation of complex cardiovascular diseases, in particular coronary artery disease (CAD) and its risk factors including diabetes, hypertension and dyslipidaemic disorders, as well as deciphering intraindividual variations in patient response to drug therapy thereof. Our general approach is first to screen for SNPs/haplotypes partly by direct sequencing the whole candidate genes for novel SNPs and partly by using established databases to identify known variants in a representative group of individuals in the general population. In the recent past, we have identified several novel and familiar single nucleotide polymorphisms (SNPs) of interest in a number of genes that we are currently evaluating for their relevance in disease. Association studies for these variants are being pursued employing the real-time PCR procedure in a population of approximately 5, 000 individuals comprising CAD patients, individuals with single or combination of risk diseases, as well as those angiographically established to have no vessel disease. During the current report period, we were able to assess the role(s) of several variants of interest in various risk genes (<10 for each gene), including in particular, myocyte-specific enhancer factor 2A (MEF2A), paraoxonase-1 (PON1), cell-restricted zinc-finger transcription factors (GATA2 and 4), protein convertase subtilisin/kexin type 9 (PCSK9) angiotensinogen (AGT) and thrombospondin). In summary, our results pointed to several haplotypes constructed from the studied variants as risk entities for CAD, its contributory genes or both. Of particular interest was the discovery that a great number of these genomic sequences constitute part of the 3 prime untranslated (3'UTR) regions for a number of genes, a finding we are chasing further with respect to the functional implications of this genomic region. We also established linkage for early onset of CAD and heterozygous familial hyperlipidaemia to various chromosomal regions in familial cases of dyslipidaemic disorders. These regions not only encompass genes that are classically linked with familial hyperlipidaemia, such as PSCK9, low density lipoprotein receptor (LDLR) or apolipoprotein B (ApoB), but also novel genes mapping on chromosomes 1 and 8 currently being investigated further for their identification and potential function. The synopse of these results is discussed below under the respective projects. In this period we also initiated five projects with collaborators both at national and international levels.

RESEARCH PROJECTS

Project title

Evaluation of the relevance of single nucleotide polymorphism for coronary artery disease in the Saudi population.

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

Project description

This study endeavours to evaluate the role of gene polymorphism(s) in CAD manifestation, using the Saudi population as a study model. This is accomplished by first identifying single nucleotide polymorphisms (SNPs) in genes of interest in the general population followed by association studies by real-time PCR procedure in a population of >5,000 individuals. These individuals may be CAD patients, or may harbor one or more of the risk diseases, such as hypertension, type 2 diabetes, dyslipidaemia in the Saudi population.

Progress

During the report period, efforts were concentrated at running the real-time PCR for previously identified variants some 11 genes of interest. In summary, the results pointed to significant association of several variants individually with CAD, or one the risk factors or both. Haplotypes constructed from these variants appeared in the majority of cases to be equally or even more significantly associated with disease than the individual variants, suggesting indeed that haplotying may be more meaningful in complex disorders. For example, while the rs3729856 (p.S377G) of GATA4 conferred risk for both myocardial infarction (MI) [Odds ratio(95% Confidence Interval) = 1.25(1.09-1.43); p=0.001] and hypertension (HTN) [1.22(1.06-1.40); p=0.005] respectively, haplotypes containing the risk G allele of this variant were equally involved in these diseases. Thus, the 5-nucletoide (5-mer) haplotypes C-G-T-C-C and C-G-T-G-A constructed from 5 of the studied variants were equally significantly associated with MI [1.32(1.11-1.57); p<0.002] and hypertension [1.28(1.07-1.54); 0.0016] respectively. Besides, some of the causative variants/haplotypes reside in the untranslated regions of the gene. This was the case, with for example the 8-mer haplotype A-G-G-A-C-G-G-A wholly resident in the 3'UTR of transcription factor MEF2A which was associated with CAD [6.39(0.93-43.75; p=0.0052), clearly indicating that changes in this genomic region play an important role in the manifestation of the disease. Similar observations were established for various variants/haplotypes from a number of other studied genes, including AGT, PON1, LDLR, PCSK9 and GATA2, to name a few. We also established that some of these genes were involved in dyslipidaemic disorders. Interesting, it appeared that different variants in the same gene may be answerable for different components of the metabolic syndromes, as in the case of PON1 in which rs3735590 [1.23(1.08-1.40); p=0.002) was strongly implicated in obesity, the rs662 [1.12(1.02-1.22); p=0.018] was associated with hyperlipidemia, while the rs854560 (p=0.031) was linked with low high density lipoprotein levels. Besides, further analysis using different inheritance model were often able to segregate between impact of recessive and dominant modes of interactions. In summary therefore, our results point to various issues of interest with respect to the potential relevance of gene polymorphisms in CAD, HTN, T2D and dyslipidaemia, which lay the basis for further investigations in possible mechanisms involved in the disease pathways in complex cardiovascular disorders.

Project title

Relevance of lipid metabolizing proteins in the treatment of hypercholesterolemia and coronary heart disease

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

Project description

This study aims at identifying mutations in candidate genes for dyslipidemic disorders as well as intra-individual differences in patient responses to drug therapy of antihypercholesterolaemia treatment with statins (lipid lowering agents). We studied the same population base employed for CAD studies. Besides, we adopted the family study approach to identify possible gene related to early onset of CAD often related to faimilial hyperlipidaemic disorders.

Progress

We initially employed the Affymetrix whole genome scan 250 sty1 array to characterize possible genomic linkage to heterozygous familial hypercholesterolemia (HFH) in 2 Saudi families of 11 and 13 individuals each, harbouring clinical features of HFH. The propositus from the first family had early onset of CAD and very significantly elevated cholesterol (Chol) level of 10.1 mmol/L and LDL-cholesterol (LDL-C) of 7.9 mmol/L as well as low HDL-C level of 0.51 mmol/L, while

4 siblings were affected with HFH. Whole genome scan for the autosomal dominant model showed high homology for the affected individuals in several regions including chromosomes 1 and 2 which harbour PCSK9 and ApoB, respectively. Subsequent sequencing of the coding regions of these two and LDLR identified 11 single nucleotide polymorphisms (SNPs) in the LDLR, 8 in the APOB and 6 in the PCSK9 genes. The propositus uniquely carried the homozygous mutant genotypes (haplotype) for all 11 LDLR SNPs, in direct contrast to the only normolipidemic sibling and a control who carried the homozygous wild type genotypes at these loci. Another set of 7 SNPs in the ApoB also isolated with HFH. Interestingly, all family members were heterozygous for all except the rs2228671 C>T of this gene, for which the mother shared the C/C genotype with the propositus, two other affected off-springs and a control, all of whom exhibited low HDL-C levels. A confirmation experiment involving 70 individuals harbouring low HDL-C revealed 74.3% of them as C/C carriers. Thus, our study identified a haplotype in the LDLR as a marker for early onset of CAD, and rs2228671 C>T in the LDLR in association with a reduction in HDL-C concentrations in FH. The results also substantiate the notion of genetic heterogeneity in HFH, underlining the essence of recognizing ethnic-specific gene variability as a potential basis for appropriate management of FH.

Project title

Clinical and molecular characterization of patients with inherited arrhythmogenic disorders

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

Project description

This study aims at identifying genes responsible for inherited arrhythmogenic disorders particularly the long QT syndrome (LQTS), Brugada and Sinus sick syndrome, in the Saudi population. This information should serve several clinical objectives including confirmation of patient diagnosis stratification and prophylactical strategies in the management of patients with arrhythmogenic disorders.

Progress

Twenty-eight Saudi families with various forms of inherited arrhythmogenic disorders (IAD) were recruited, of which 13 had Romano-Ward syndrome (RWS), 5 had Jervell and Lange-Nielsen 4 with Brugada, 2 with sick sinus syndrome, 3 with arrhythmogenic right venricular dysplasia and 1 with catecholaminegic polymorphic ventricular tachycardia. Several genes known to be associated with IAD were tested in these families. In summary, 5 families harboured heterozygous mutation in KCNQ1 and 1 in PKP2, 4 families showed homozygous mutations in KCNQ1, I in CASQ1 and 1 SCN5A genes. These data thus far represents the largest cohort of Arab patients and illustrates the impact of high degree of consanguinity on causative genotypes for IAD.

Project title

Evaluation of camel milk and urine in treatment of diabetic and cardiovascular diseases

Investigators: Nduna Dzimiri, Salma Wakil, Maha Al-Rasheed, Ali Zharani

Project description

The potential of using camel milk as a therapeutic entity has been recognized since centuries ago, leading to its consumption for such purposes particularly among the Middle Eastern populations. Understandably, as the only natural source of nutrients in the early stages of life, milk contains the constituent elements of all three components essential for mammalian existence, i.e., proteins (e.g. lactoferrin, lactoperoxidases, lysonzymes), carbohydrates (lactose) and fats (linoleic acid), as well as essential minerals, such as calcium, phosphorus and magnesium required for mammalian development. Besides, it harbours the natural components for providing the foetus with protection against possible infection, before its own immune system matures. In the Middle Eastern countries in particular, there is a traditional belief that regular consumption of camel milk may aid in prevention and control of diabetes. However, the currently available literature on this subject appears to be more assertions of old postulations rather than scientifically proven therapeutic management of disease. The existing literature seems to suggest that camel milk can prevent or be employed to treat type 1 diabetes mellitus (T1D). However, controversy still reigns with regards to several issues pertaining to these actions. Among others, for example, it remains unclear as to whether it is specifically camel milk, if at all, that exhibits these actions or could any other type of milk exert the same effects, in general. In this study therefore we would like to investigate whether camel milk and urine have the purported effects on diabetes and cardiovascular disease, and if so, what components might be responsible for such actions.

Progress

This a novel project in its early infancy.

Project title

The role of gene polymorphism in the regulation of the thyroid stimulating hormone level

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

Project description:

The levels of thyroid hormones in circulation are tightly regulated by a feedback control system in which changes in the serum thyroid hormone levels induce inverse changes in the serum level of TSH; i.e. hyperthyroidism suppresses TSH secretion while hypothyroidism stimulates it. The normal serum TSH level ranges between 0.5-5.0 U/l. This range is relatively wide and it is not quite clear what determines this hormone level in an individual. It is likely that pharmacogenomics will further characterize some additional factors involved in the variability of TSH level between individuals. Besides, recent studies have shown a clear association between the risk of differentiated thyroid cancer (DTC) and the high TSH level within normal range. In this study, we attempt to test first the hypothesis that TSH levels are related to presence of variations in one or more genes that are involved in its messenger RNA production, metabolism, transport or actions of thyroid hormones by studying the relationships of TSH and thyroid hormone levels and polymorphisms in thyroid stimulating hormone, beta (TSHB), iodothyronine deiodinase types I, II, III DIO1, DIO2, DIO3), and sodium/iodine symporter (NIS), paired box gene 8 (PAX8) in subjects who have no evidence of thyroid disease. If we find a clear correlation between high normal TSH and gene polymorphism, we will test the hypothesis that this polymorphism may act as a genetic marker for increased predisposition to differentiated thyroid cancer (DTC). To test this, we will screen for the same polymorphism found in phase 1 comparing its incidence in patients who had DTC to its rate in age- and sex-matched healthy individuals in a case control design. At the end of this study, we hope to demonstrate that (1) the high normal TSH level is related to the presence of a gene polymoprphism(s) which not only predicts TSH levels but also serve as a genetic marker for the high normal TSH-associated risk of DTC.

Progress:

Some four hundred DTC patients have been recruited and are currently being studied.

Project title

Role of the scaffold protein striatin in regulating cardiac remodelling

Investigators: Moni Nader, Nduna Dzimiri and Dana Bakheet

Project description

Striatin is a scaffold protein originally discovered in neuronal membranes with high adenylyl cyclase activity, but its role remains to be defined. The protein harbours dynamic stretches including (a) coiled-coil motif, (b) eight WD repeats, (c) caveolin binding domain and (d) calmodulin binding sites. In vascular endothelial cells, this protein assists in the assembly of membrane signalling complexes by anchoring to the oestrogen receptor and eventually modulating signal transduction. It probably also serves as a scaffold protein within a multicomplex network of kinases and phosphatases primarily consisting of Mob3, GCK, CCM, PP2A. The ultimate outcome of the signalling pathways regulated by these kinases and phosphatases suggest mutlifunctional roles for striatin within the cell (i.e. cell death, cell growth, proliferation, cell cycle). In fact, signalling pathways regulated by striatin partners were reported to be activated during cardiac remodelling and/or contraction. For example, the oestrogen receptor was reported to activate the MAP kinase pathway, aberrant activation of which leads to cardiomyocyte growth and hypertrophy leading to cardiac dysfunction, which is suggestive of a pivotal role for striatin myocardial remodelling. During cardiac development, the remodelling program is highly active in order to accommodate for the demand. Cardiomyocytes stop dividing shortly after birth and undergo enormous changes including increased cell size. This is facilitated by activation of signalling cascades and regulatory proteins involving growth receptors, protein synthesis and calcium homeostasis. Similalry, the foetal gene program is re-activated following myocardial infarction, thus leading to hypertrophy and consequently impaired cardiac function. Although striatin was reported in different tissues and cell lines, there is a dearth of information on its presence and/or role in cardiomyocytes. While recent reports showed an association of arrythmogenic right ventricle tachycardia with a deletion of the 3' untranslated region of striatin gene

resulting in less mRNA production, biochemical analysis revealed that the interaction between striatin and calmodulin or caveolin is calcium sensitive. This is suggestive of an important role for striatin in regulating cardiomyocytes dynamics. Having successfully identifying striatin in the heart, we are proposing to study its role in the evolution of cardiac remodeling by studying its expression level during normal cardiac development with emphasis on its molecular aspects in regulating myocardial remodelling. We will be manipulating the levels of striatin by employing knock down and overexpression procedures and evaluate the status of the multi-signalling complex assembled by striatin to better understand the role of this scaffold protein in regulating cardiomyocyte function.

Progress

Work began some two months ago.

PUBLICATIONS

ORIGINAL PEER-REVIEWED FULL-LENGTH PAPERS

- Abu-Amero KK, Al-Boudari OM, Mousa A, Gonzalez AM, Larruga JM, Cabrera VM and Dzimiri N, The mitochondrial DNA variant 16189 T>C is associated with coronary artery disease and myocardial infarction in Saudi Arabs. *Genetic Testing and Molecular Biomarkers*, 14, 43-7, 2010.
- Elhawar S, Al-Boudari O, Muiya P, Khalak H, Andres E, Al-Shahid M, Al-Dosari M, Meyer BF, Al-Mohanna F and Dzimiri N. A study of the role of the myocyte-specific enhancer factor-2A gene in coronary artery disease. *Atherosclerosis*, 2010.

ABSTRACTS AND SCIENTIFIC CONFERENCE PROCEEDINGS

- Al-Rasheed MM, Al-Najai M, Mary Vigilla MG, Wakil S and Dzimiri N. The rs10934857T>C of the GATA2 gene is a susceptibility variant for myocardial infarction. 60th Annual Meeting of The American Society of Human genetics, Washington DC, November 2-6, 2010.
- Baz B, Vigilla MG, Alboudary O, Muiya P, Andres E, Alshahid M, Wakil S and Dzimiri N. The rs854560 variant of the PON1 predisposes individuals to harbouring low high density lipoprotein levels. 60th Annual Meeting of The American Society of Human genetics, Washington DC, November 2-6, 2010.
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- Alrasheed MM, Muiya P, Wakil S, Al-Najai M, Andres E, Mazher N, Dzimiri N. The rs2228671C>T of the LDLR gene confers risk for low HDL and early onset of coronary artery disease. Experimental Biology 2010, Anaheim, CA, April 24-28, 2010.
- Alrasheed MM, Muiya P, Gueco D, Andres E, Al-Shahid M and Dzimiri N. The Ser377Gly of the GATA4 gene is a susceptibility variant for hypertension. Experimental Biology 2010, Anaheim, CA, April 24-28, 2010.
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Cognitive Genetics

Head
Namik Kaya, MSc, PhD

Members
AlBandary AlBakheet, MSc
Banan AlYounes, MSc

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

MISSION AND GOALS

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

Though our unit is recently established, we have initiated several multidisciplinary research projects including international collaborations with Harvard International and Newcastle University in UK. Our current projects focus on positional cloning of genes underlying genetic disorders with prominent neurodevelopmental manifestations, dysmorphia and mental retardation. We also focus on detection of chromosomal abnormalities as well as copy number variations (CNVs) found among patients and normal individuals. One of the exciting projects undertaken by our unit is creation of a database including such malignant and benign CNVs.

RESEARCH PROJECTS

Project title

Positional Cloning of genes underlying genetics disorders with prominent neuro-developmental manifestations in several extended families" (RAC# 2060 035)

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

Project description

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

Progress

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

Project title

Genetic Basis of Mental Retardation in Families from KSA (RAC# 2080-036).

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

Project description

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

Progress

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

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

Project title

Molecular genetic studies in chromosome disorders. RAC #2040 042.

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

Project description

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

Progress

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

Project title

Pathogenesis of Early Infantile Primary Lactic Acidosis. RAC # 2050-009

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

Project description

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

Progress

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

International Collaborator: Robert W. Taylor, Mitochondrial Group, Newcastle University, Newcastle upon Tyne, UK

Overall, we have had 16 peer-reviewed journal articles, one peer-reviewed review article and a book chapter published in high-impact factor journals and a prestigious publisher's book. from May 2008 to May 2011.

RECENT PUBLICATIONS

Book Chapters

- Surendran S, Kaya N, Ozand PT, Canavan Disease: Molecular Pathology, Phenotype and Therapeutic Approaches. In: Neurochemistry of Metabolic Diseases Editors: Sankar Surendran, ISBN 978-1-61209-671-1, © 2011 Nova Science Publishers, Inc.

Review Articles in Peer Reviewed Journals

- Kaya N, Colak D, Ozand P. Autism spectrum disorders: a review. Trends in Developmental Biology, 2007, Vol 2. p: 74-94

Research Articles Published in Peer Reviewed Journals

- Kaya N, Al-Owain M, AbuDheim N, AlZahrani J, Al-Hassnan Z, Rahbeeni Z, Al-Sayed M, Muheizea M, Colak D, Milanlioglu D, Ozand PT, Alkuraya FS. GM2 Gangliosidosis in Saudi Arabia: Can New York Success Story be Replicated? *American Journal of Medical Genetics A*. 2011 May 12. doi: 10.1002/ajmg.a.33932 [Epub ahead of print].
- Al-Zahrani J, Al-Dosari N, AbuDheim N, Alshidi TA, Colak D, Al-Habit O, Sakati N, Ozand PT, Meyer B, Kaya N. Chromosome 12q24.31-q24.33 deletion causes multiple dysmorphic features and developmental delay: First mosaic patient and overview of the phenotype related to 12q24qter defects. *Molecular Cytogenetics* 2011 Apr 2;4:9. PMID: 21457577 [PubMed - in process].
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- Al-Owain M, Kaya N, Al-Zaidan H, Bin Hussain I, Al-Hindi H, Kennedy S, Iqbal MA, Al-Mojalli H, Al-Bakheet A, Puel A, Casanova J-L, Al-Muhsen S and Al-Manea H. Renal Failure Associated With APECED and Terminal 4q Deletion: Evidence of Autoimmune Nephropathy. *Clinical and Developmental Immunology* 2010 Volume 2010, Article ID 586342, 7 pages doi:10.1155/2010/586342.
- Kaya N, Al-Muhsen S, Al-Saud B, Al-Bakheet A, Colak D, Al-Ghonaium A, Al-Dhekri H, Al-Mousa H, Arnaout R, Al-Owain M, Iqbal M. ICF Syndrome in Saudi Arabia: Immunological, Cytogenetic and Molecular Analysis. *J Clin Immunol*. 2010 Dec 1. [Epub ahead of print] PubMed PMID: 21120685.
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- Al-Owain M, Kaya N, Al-Zaidan H, Al-Hashmi N, Al-Bakheet A, Al-Muhaizea M, Chedrawi A, Basran R, Milunsky A. Novel intragenic deletion in OPHN1 in a family causing XLMR with cerebellar hypoplasia and distinctive facial appearance. *Clin Genet*. 2010 May 7. [Epub ahead of print] PubMed PMID: 20528889.
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Recent Conference Presentations

- Kaya N, Al-Zahrani J, Al-Dosari N, Colak D, Al-Sheddi T, Al-Habit O, Meyer B, Ozand P, Sakati N. Molecular Characterization of a Chromosome 12q Telomeric Terminal Deletion in a Patient with Dysmorphia. ASHG 2009 Honolulu, HI, USA
- Al-Owain M, Colak D, AlBakheet A, AlYounes B, AlFadhli F, Al-Hashem A, Al-Odaib A, Faiyaz-Ul-Haque M, Al-Hassnan Z, AL-Zeydan H, Al-Rahbeeni Z, Al-Sayed M, Al-Alaiyan S, K. Abu-Amero KK, Ozand PT, Kaya N. Mutation analysis and genome-wide gene expression profiling on patients with primary lactic acidosis. ASHG 2009 Honolulu, HI, USA.
- Colak D, Chishti MA, AlBakheet A, Al-Qahtani A, Shoukri M, Goyns M, Ozand P, Quackenbush J, Park BH, Kaya N. Integrative and comparative genomics analysis of early hepatocellular carcinoma differentiated from liver regeneration in young and old. ASHG 2009 Honolulu, HI, USA.
- 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.
- 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. HDM-2008 International Conference on Multivariate Statistical Modeling & High Dimensional Data Mining, June 2008, Kayseri, Turkey.
- 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
- Colak D, Kaya N, AlBakheet A, Alyounes B, Al-Odaib A, Meyer B, Nester M, Ozand P, Sakati N. Molecular and bioinformatics analysis of osteopetrosis with renal tubular acidosis (OPRTA) subtypes: Classic OPRTA, OPRTA with autism, and OPRTA with mental retardation. The Pacific Symposium on Biocomputing (PSB) 2009. January 5-9, 2009. The Big Island of Hawaii.
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- 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.
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Computational Genetics

Head

Hanif Khalak

Members

Staff recruitment is in progress.

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.

RESEARCH PROJECTS

Project title

Genome-Wide Association Study (GWAS) of chronic hepatitis B (HBV) infection in Saudi population in collaboration with BMR and KSU.

Investigators: H.G. Khalak, F. Al-Kuraya (GEN), A. Al-Qahtani (BMR), A. Abdu (KSU).

Project description

Prevalence and progression of hepatitis infections is of great clinical and research importance in Saudi Arabia, as it is world-wide. This work involves the investigation of a panel of SNPs in a genome-wide association study (GWAS) across almost 1000 patients (total cases and controls) with chronic HBV infection and associated secondary diagnoses such as cirrhosis and hepatocellular carcinoma (HCC). This GWAS will be the first one to be completed in the Middle East. Application of bioinformatics and statistical genetics ranges from SNP genotype data manipulation and QC, population stratification identification and removal, calculation of allelic and genotypic association statistical significance, linkage disequilibrium analysis, as well as annotation and visualization of genomic regions for implicated loci.

Progress

GWAS analysis procedures have been completed using tools such as Partek Genomics Suite and plink, and results from this study are being finalized and a manuscript prepared for submission.

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 enhanced to handle the large ongoing genome-wide studies both for SNP genotyping (HBV, cancer, CPR) and next-generation sequencing (NGS). 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. Storage capacity has been doubled to 40TB with capability to add another 100TB. 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 successfully migrated to use this computing infrastructure.

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 has been completed and improved network performance >500% for RC servers. Subsequent plans include and upgrade of internet bandwidth for RC servers and users.

Phase II: ITA has completed upgrade of all KFSH&RC switches to Cisco 3750, and configuration of network between Genetics servers in ITA and systems in RC have been improved providing additional performance.

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 with respect to hardware, networking, data management, and client access. Working with system vendors (Perkin-Elmer, HVD Systems), ITA, and BESC Computer Support, the NBS team's goal is to provide 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

Several operational meetings with system vendors identified new workflows and enhancements were made to query and access LIMS information. In addition, a web site was developed providing query and reporting access to Newborn Screening data on a secure, per-client institution basis. Additionally, detailed work was performed to produce a request for proposal (RFP) for a major redesign of the PSCDR and NLNBS web site, in order to present related projects and accommodate mobility and remote-access requirements.

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 as well as a number of papers related to homozygosity mapping to find disease genes are under review.

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) has been submitted and is under review.

Project title

Association Analysis for Case-Control Cardiovascular and Metabolic Disease 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 GATA4, PON1, GATA2). Successful application of modules using statistical 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). In addition, work has begun to perform a genome-wide association study (GWAS) in a large Saudi case-control cohort.

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 of H5N1, H1N1, HBV and HCV, and identify and confirm important sites in viral proteins. We are in the process of performing follow-up 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. *Genome Research*, submitted.
- 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*. 2010 Mar;209(1):152-4.

Local Conferences and Meetings

Presented lecture on Bioinformatics of Cardiovascular Genetics at Prince Salman Heart Congress, June 2010.

Training Courses taught

7-9/03/2011 - Bioinformatics of Sequence Analysis (13 CME credits), ~50 registered and paid students

Developmental Genetics

Head

Fowzan Alkuraya, MD

Members

Anas Alazami, DPhil
Mohamed Aldahmesh, PhD
Leen Abu Safieh, PhD
Ranad Shaheen, PhD
Mohammed Al-Dosari, PhD
Hanan Shamsheldin
Lama Al-Abdi
Fatma Al-Zahrani
Mais Hashem
Jawahir Yousuf Nur
Shams Anazi
Nouran Adly
Tarfa Sheddi

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.

RESEARCH PROJECTS

Project title

Genetics of Vision Loss in Saudi Arabia

Project description

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.

Project title

Genetics of Craniofacial Birth Defects in Saudi Arabia.

Project description

This is both DHFMR- and KACST-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.

Project title

MERTK Gene Therapy for Retinal Degeneration: This is a PSCDR-funded project in which we aim to treat human patients with MERTK-related retinal degeneration using gene therapy.

Project title

Carrier Phenome Project

Project description

This is a KACST-funded project in which we aim to systematically investigate carriers of deleterious recessive mutations for possible increased risk of common phenotypes.

Project title

In Search of the Genetic Determinants of Diabetic Retinopathy

Project description

This is a KACST-funded project in which we aim to identify the genetic risk loci of diabetic retinopathy using GWAS approach.

Project title

Genetics of SLE

Project description

In this project we study Mendelian phenocopies of SLE to identify novel risk genes.

Project title

Positional Cloning of Developmentally Relevant Genes Using Patients with Balanced Chromosomal Rearrangements

Project description

This is a positional mapping project that involves the study of breakpoints in patients with balanced rearrangements.

Project title

Clinical, Biochemical and Molecular Characterization of Perxoisomal Diosrders in Saudi Arabia.

PUBLICATIONS

Peer Reviewed Journals

- Saadi I, Alkuraya FS, Gisselbrecht SS, Goessling W, Cavallesco R, Turbe-Doan A, Petrin AL, Harris J, Siddiqui U, Grix AW, Hove HD, Leboulch P, Glover TW, Morton CC, Richieri-Costa A, Murray JC, Erickson RP, Maas RL. Deficiency of the Cytoskeletal Protein SPECC1L Leads to Oblique Facial Clefting. *Am J Hum Genet*. 2011 Jun 22.
- Almaghlouth I, Mohamed J, Al-Amoudi M, Al-Ahaidib L, Al-Odaib A, Alkuraya F. 5-Oxoprolinase deficiency: report of the first human OPLAH mutation. *Clin Genet*. 2011 Jun 8.
- Aldahmesh MA, Nowilaty SR, Alzahrani F, Al-Ebdi L, Mohamed JY, Rajab M, Khan AO, Alkuraya FS. Posterior microphthalmos as a genetically heterogeneous condition that can be allelic to nanophthalmos. *Arch Ophthalmol*. 2011 Jun; 129(6):805-7.
- Kaya N, Owain MA, Abudheim N, Zahrani JA, Colak D, Sayed MA, Milanlioglu A, Ozand PT, Alkuraya FS. GM2 gangliosidosis in Saudi Arabia: Multiple mutations and considerations for future carrier screening. *Am J Med Genet A*. 2011 May 12.
- Seidahmed MZ, Alkuraya FS, Shaheed M, Al Zahrani M, Al Manea W, Mansour F, Mustafa T, Farid G, Salih MA. Ritscher-Schinzel (cranio-cerebello-cardiac, 3C) syndrome:

Report of four new cases with renal involvement. *Am J Med Genet A*. 2011 May 12.

- Shaheen R, Al-Owain M, Faqeih E, Al-Hashmi N, Awaji A, Al-Zayed Z, Alkuraya FS. Mutations in FKBP10 cause both Bruck syndrome and isolated osteogenesis imperfecta in humans. *Am J Med Genet A*. 2011 May 12.
- Alkuraya FS, Cai X, Emery C, Mochida GH, Al-Dosari MS, Felie JM, Hill RS, Barry BJ, Partlow JN, Gascon GG, Kentab A, Jan M, Shaheen R, Feng Y, Walsh CA. Human Mutations in NDE1 Cause Extreme Microcephaly with Lissencephaly. *Am J Hum Genet*. 2011 May 13; 88(5):536-47.
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- Khan AO, Aldahmesh MA, Alkuraya FS. Genetic and genomic analysis of classic aniridia in Saudi Arabia. *Mol Vis*. 2011; 17:708-14.
- Khan AO, Aldahmesh MA, Al-Abdi L, Mohamed JY, Hashem M, Al-Ghamdi I, Alkuraya FS. Molecular Characterization Of Newborn Glaucoma Including A Distinct Aniridic Phenotype. *Ophthalmic Genet*. 2011 Feb 9.
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First Arabian Hereditary Deafness (FAHD) Unit

Head

Faiqa Imtiaz Ahmad, PhD

Members

Khushnooda Ramzan, PhD
Danyah Trabzuni (PhD Student)
Bashayer Al-Mubarak (PhD Student)
Rabab Allam
Abeer Al Mostafa
Lolowa Jumaa
Mosaab Doubi

The primary functions ot the First Arabian Hereditary Deafness Unit are:

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.

RESEARCH PROJECTS

Project title

Molecular Characterization of Hereditary Deafness in Saudi Population (KACST#08-MED495-20: RAC# 2100 001).

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

Project description

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

Progress

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

Project title

Clinical and Molecular Basis of Laron Syndrome Patients in Saudi Arabia (RAC# 2101 034):

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

Project description

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

Progress

We have currently found the disease-causing mutation in 36 of the 40 patients enrolled in this study.

PUBLICATIONS

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Genotyping Core Facility

Members

Salma Wakil, PhD
Batool Baz, MSc
Samiya Hagos, Bsc (Grant)
Haya Al Dusery, Bsc (Grant)

The main aim of this unit is to provide genotyping for DNA Analysis and differential Gene Expression profiling using the Affymetrix GeneChip technology, accelerating the genetic research and enables the researchers to develop the diagnostic tools and tailor treatments for individual patients by identifying and measuring the genetic information associated with mendelian and complex disorders.

Besides the GeneChip Stations, the laboratory is equipped with high throughput workflow which enables us to process approx. 760 samples in two weeks time with Axiom Genome Wide Human Array Plate. The Axiom genotyping solution is the newest line of product which enables to perform population optimized genome wide association studies, replication studies and candidate gene studies.

This fully automated workflow utilizes GeneTitan Multi Channel (MC) instrument and automated target preparation on the Beckman Biomek FX Target Prep Express system.

Besides providing data for mapping mendelian disorders, we are doing large association studies for Coronary Artery Disorders and Hepatitis B & C Virus association studies.

We are running the cytogenetic microarray which is again a high resolution array to detect broad range of chromosomal aberrations, detects uni-parental disomy and regions that are identical by descent.

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

Project title

Molecular Genetic Characterization of Hereditary Spastic Paraplegias (HSPs). In this number of families have been collected and linkage analysis has been done. In at least, 4 families we have identified the mutation causing the disease in these families and further more families are being collected that would be subjected to axiom genome wide mapping array for homozygosities and eventually screening for mutation detection.

Project title

Mapping of X-linked diseases with mitochondrial abnormalities.

Project description

This project was successfully completed with the underlying gene mutation responsible for this disorder where whole whole genome scanning was done using affymetrix 250styI for the family of three affected cases. Based on linkage results sequencing of the FGD1 gene which encodes Rho/Rac guanine exchange factor (GEF) was done. A nonsense mutation was identified in all affected individuals fully consistent with an X-linked pattern of inheritance. A paper has been submitted for publication purpose.

Project title

Clinical and molecular characterization of patients with inherited arrhymogenic disorders.

Project description

This project is in collaboration with pharmacogenetics unit where the candidates genes involved for LQT and other arrhythmogenic disorders are screened and whole genome scanning is done for 4 families.

Project title

Localization of Familial Juvenile Rhematoid Arthritis.

Project description

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

Project title

Identifying the chromosomal location of the gene underlying a novel autosomal recessive syndrome of myopathy.

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. We could not identify the mutation in some potential candidate genes. We have send the samples to the Sequencing core for Whole Genome Sequencing with the help of Solid instrument from ABI. And hopefully together with our linkage results, we will be able to identify the gene underlying this disorder.

ImmunoGenetics

Head
Brian Meyer

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

RAC-APPROVED RESEARCH ACTIVITY

Project title

Underlying Genetics of Familial Hemophagocytic Lymphohistiocytosis (FLH) in Saudi Arabia, RAC No. 2080 041.

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

Project description and progress

Hemphagocytic Iymphohistiocytosis (HLH) is a serious immune disorder characterized by a severe hyperinflammation on top of various inherited or acquired immunodeficiencies. The hallmark of the disease is an impaired or absent function of natural killer (NK) cells and cytotoxic T cells (CTL). Familial Hemophagocytic Lymphohistiocytosis (FHL) is an autosomal recessive condition in which several genetic defects have been identified. Studies in recent years have revealed the underlying genetic defects in some forms of FHL. These findings have provided an explanation for the defective cytotoxic cell function in FHL. Molecular defects of Saudi patients with FHL are unknown. This study is going to elucidate the genetic defects in this subgroup of patients. Conducting this study is critically needed because of the increasing incidence of the disease due to the high consanguineous marriage rate in Saudi Society. Also knowing the molecular defects in FHL Saudi patients will be of tremendous value in the diagnostic confirmation in symptomatic individuals, screening of the related-bone marrow donors prior to Stem Cell Transplantation, presymptomatic diagnosis of at-risk siblings, identification of carriers, prenatal diagnosis, preimplantation Genetic Diagnosis (PGD) and genetic counselling

Project title

Underlying molecular genetic defects of Primary Immunodeficiency Diseases in Saudi Arabia, RAC No. 2080 025.

Investigators: Dr. Hamoud AI-Mousa, Dr. Abbas Hawwari, Dr. Abdulaziz AI-Ghonaium, Dr. Hasan AI-Dhekri, Dr. Saleh AI-Muhsen, Dr. Rand Arnaout, Dr. Bandar AI-Saud, Dr. Dorata Monies, Mr. Mohamed AI-Hamed.

Project description and progress

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

Project title

Transcriptional Regulation of TCRα/δ Locus, RAC No. 2080 019.

Investigators: Dr. Abbas Hawwari, Dr. Goran Matic, Dr. Edward Hitti

Project description and progress

Humeral immunity depends on the generation of diverse repertoire of immunoglobulin (Ig) and T-cell receptor (TCR). For this to happen, mature Ig and TCR genes are generated by the rearrangement of one of each of the Variable (V), Diversity (D), and Joining (J) gene segments by the process of V(D)J recombination. Each gene segment is flanked by Recognition Signal Sequences (RSS). This process occurs during lymphocyte development, as well as in response to exogenous stimuli and it is tightly controlled, so that it is restricted to the appropriate cell lineage and stage of development. Recombination is initiated by DNA breaks

mediated by Rag1 and Rag2 proteins at two RSS borders which the normal rejoining process resolves both sets of DNA ends efficiently. Failure of the normal rejoining triggers cellular DNA damage sensors leading to cell death and the prevention of oncogenic transformation. Impairment of these responses may allow alternative DNA repair pathways to mediate rejoining of antigen receptor genes with sites elsewhere in the genome. This breach on DNA integrity may lead to lymphoma-associated chromosomal translocations, which is a central feature of neoplasms in the immune system such as non-Hodgkin's lymphoma (NHL) and acute leukemia. 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. To do that we have been characterizing five promoter elements that associate with different gene segments and dictate at what stage of T cell development these segments are activated.

Project title

RORγt role in T cell development, autoimmunity and transformation, RAC No. 2080 046.

Invistigators: Dr. Abbas Hawwari, Dr. Namik Kaya, Dr. Dilek Colak, Dr. Goran Matic

Project Description and Progress

RORγt, a member of the hormone nuclear receptor super family, is a transcription factor that activates or suppresses many genes. The function of RORγt was studied in multiple mouse models that are deficient in RORγt. RORγ-/- mice lack both RORγt and RORγ (an isoform variant of RORγt) and RORγtGFP/GFP mice (do not express RORγt but express EGFP instead). These mouse models showed that RORγt expression is restricted exclusively to a limited number of cell types in the immune system, specifically; double positive (DP) thymocytes, lymphoid tissue inducer (LTi), crypto patches (CP), isolated lymphoid follicles (ILF), and T helper -17 (Th17) cells. RORγt was shown to be indispensible for the development of secondary immune organs such as Peyers patches (Pp), and lymph nodes (LN). Other defects due to RORγ loss are also observed: proliferation/apoptotic defects in DP thymocytes, inefficient DP thymocytes development, lack of CP and ILF, enlarged spleen and absence of Th17 cells. Moreover, RORγt is involved in the development of autoimmune diseases and thymic lymphoma. Our knowledge of the molecular mechanism by which RORγt controls the development of immune cells, organs and structures and protect against autoimmunity and thymic lymphoma is lacking. We think that in order to understand these processes, we need to understand: first, what controls RORγt expression and why it is restricted to only small numbers of immune cell types, second, the genes that are regulated by RORγt and third, what proteins interact with RORγt to facilitate its function. This knowledge will help us understand, not only the development of DP thymocytes, LN, Pp, CP, ILF, and Th17, but also the process by which RORγt protects us against autoimmune and lymphoma diseases. On the long run, this information will help in the diagnosis, drug design and treatment of such diseases in a similar fashion to the success story with estrogen receptor and breast cancer. We have just started on this project and we currently doing the necessary cloning and developing reagents such as antibodies.

Project title

Underlying molecular genetic defects of the Dystrophic Epidermolysis Bullosa Diseases in Hail, Saudi Arabia, RAC No. 2100 008.

Invistigators: Dr. Abbas Hawwari, MS. Badriah Awad Manahi AL-Shammari, Dr. Entissar AL-Suhaibani.

Project Description and Progress

Epidermolysis bullosa (EB) is a condition characterized by blistering of the skin and mucous membrane after minor traumas. Four types have been described: simplex, junctional, hemidesmosal and dystrophic. In this study, we will focus on the genetic causes of the dystrophic (DEB) form. DEB results from the genetic defects of the COL7A1 gene encoding type VII collagen which has been extensively studied in different populations around the world including Middle Eastern populations. These studies showed that the mutations affecting the Middle Eastern populations are substantially different than the rest of the world. Unfortunately, research studies of the molecular epidemiology of EB is lacking in Saudi Arabia. Only one study has been described for the eastern province of Saudi Arabia. So, it is critically important to undergo molecular genetic studies of DEB in Saudi Arabia as such studies will help the affected families and health authorities for proper management of the disease. Our study will focus on a cohort of families affected by the disease that reside in Hail area. We will compare DNA sequences extracted from the blood of affected individuals and their unaffected relatives to identify changes that can explain the clinical presentation of the disease. Additionally we will compare the mutations that affect the Saudi population to those reported internationally.

National Laboratory for Newborn Screening (NLNBS)

Head

Ali Al-Odaib PhD

Members

Ayman Al-Sulaiman PhD
Amal Saadallah, MD, PhD
Mohammad Al-Amoudi
Faisal Al-Otaibi
Fahd Al-Badaoui
Minnie Jacob
Lujane Al-Ahaidib
Ahmad Al-Odaib
Khaled Al-Qahtani
Manhal Al-Mokhadab
Basma Al-Rasheed
Jawaher Al-Saud
Maria Elena Bernabe
Cynthia Laureles
Rana Akili
Bindhu Kumari
Ebtesam Jambi
Ebtessam Al-Humaidi
Lolowa Jomaa
Emalyn Samonte
Amera Al-Hafi

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 2010. The number of screened newborns by the program increased to more than one hundred ten thousand (110,000). 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.

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.

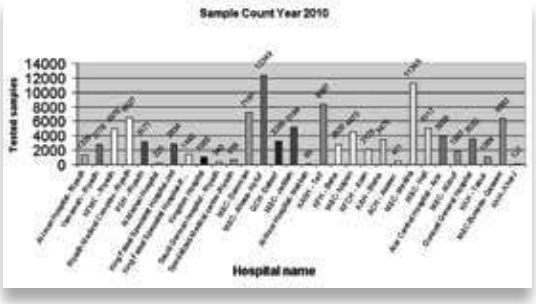
The program targets three hundred thousand (300,000) newborns from two hundred forty (240) birth center in different regions of KSA. The program includes screening dried blood spots from newborns at 24-72 hours after birth for sixteen (16) inherited metabolic and endocrine disorders (see list below).

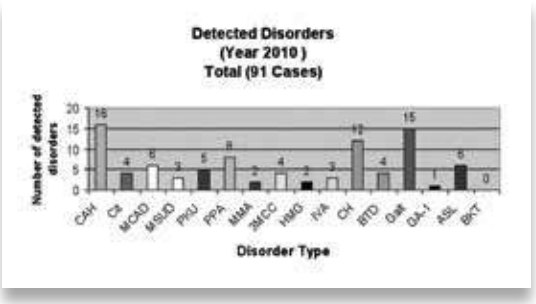
- Phenylketonuria (PKU)
- Maple Syrup Urine Disease (MSUD)
- Arginosuccinase Deficiency (ASL)
- Citrullinemia (ASD)
- HMG-CoA Lyase Deficiency (HMG)
- Isovaleric Acidemia (IVA)
- Methylmalonic Acidemia (MMA)
- Propionic Acidemia (PA)
- Beta-ketothiolase Deficiency (BKT)
- Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)
- Glutaric Acidemia type-I (GA-I)
- Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
- Galactosemia (GAL)
- Congenital Hypothyroidism (CH)
- Congenital adrenal Hyperplasia (CAH)
- 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 2010, 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 2010, NLNBS managed to screen more than hundred and ten thousand (110,000 babies) and more than fifty thousand specialized diagnostic assays. In total, the Laboratory performed more than six hundred fifteen thousand (615,000) different tests in 2010. Ninety one (91) babies were found to be affected yield to a total of 502 affected newborn were detected since the start of the program. The incidence for the 16 screened diseases was 1:1000. 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 2011-2012.





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.

Projec title

Replication for Genetic Association Studies on Birth Weight and Gestational Age, (RAC# 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.

Projec 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.

Projec 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# 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

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

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

Saudi Diagnostics Laboratory

Head

Brian F. Meyer, PhD

Members

Nabil Moghrabi, PhD
Amr Al Saif, MD, dABMG
Dorota Monies, PhD
Mohammed Al Hamed, MSc
Rana Al Omar, MSc
Alaa Doubi
Ola Khashogji
Huda Al Ajlan
Heba Al Ruwaili
Amal Jaafar
Rula Abouthuraya
Sara Al-Haibey

In 2010 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. It focuses on the identification of 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 2010.

SDL now performs a repertoire of over 200 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 2010 in excess of 200 requests for molecular karyotyping were processed and this continues to be a growth area. Animal genetics is 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.

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 2010 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 120 cases having been processed in 2010.

Sequencing Core Facility

Head

Dorota Monies, PhD

Members

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

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.

SERVICES OFFERED

DNA Purification

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

DNA Sequencing

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

Objective Quality Controls

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

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

Subjective Quality Controls

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

ADDITIONAL SERVICES

Fragment analysis

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

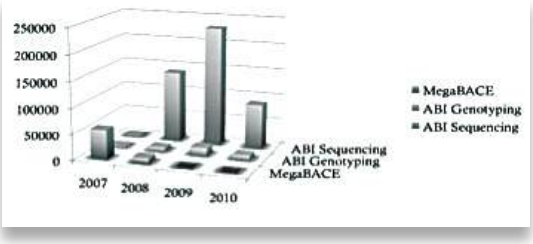
Oligo orders

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

RESEARCH PROJECTS/ACTIVITIES

The Unit is involved in a broad range of medical scientific and diagnostic work, contributing to most of the research projects carried out in the Department of Genetics. Core cooperates with 71 researches within the Research Center and also from outside e.g. the King Saud University. In last year we generated approximately 16,000 genotyping results and 240,000 sequencing reads.

Number of samples in SCF



DNA Sequencing Requirements:

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

1. **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 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.

THE

Human Cancer Genomic Research

The Human Cancer Genomic Research

Director

Khawla S. Al-Kuraya, MD FCAP

Staff

Scientific Staff

Hassan Al-Dossari
Maha Al-Rasheed, BSc
Maqbool Ahmed, PhD
Aisha Alyan, BCh
Valorie Balde, BSMT
Rong Bu, MD, PhD
Wael Haqawi, BSc
Zeenath Jehan, PhD
Sarita Prabhakaran, MD
Nurul Hassan Shaikh, BDS
Mehar Sultana, MSc
Khadija Al-Obaisi, BSc
Jehad Abubaker, PhD
Saeeda Ahmed, BSc
Padmanabhan Annaiyappanaidu, BSMT
Prashant Bavi, MD
Thara George, BSN
Azhar R Hussain, MBBS
Shahab Uddin Khan, PhD
Syed Zeeshan Qadri, MSc
Abdul Khalid Siraj, PhD
Saravanan Thangavel, MSc

Administrative Staff

Saad Al-Odaib
Maria Victoria Concepcion
Selah Fulgencio
Myra Maningas

The mission of Human Cancer Genomic Research (HCGR) is to conduct translational research on cancers that are more prevalent in the Kingdom of Saudi Arabia. The main focus of the Research 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.

Year 2010 has been another productive year for the Human Cancer Genomic Research (HCGR), during which many new scientific accomplishments were achieved. First and foremost, HCGR was able to obtain the HiSeq Illumina sequencer, a state of the art sequencing instrument that will be used extensively to characterize cancers of Middle Eastern origin. With this technique, new avenues of cancer research will be explored and this will improve the diagnostic and prognostic criteria of cancer. In addition, this may also improve the therapeutic modalities of these cancers by identifying new targets for intervention. For the first time in the history of KFSHRC, 24 abstracts were submitted and accepted for presentation in the 2011 American Association of Cancer Research annual meeting that is being held in Orlando, Florida from the 2-6 April 2011. This is indeed, a great accomplishment that shows the productivity of HCGR. We were able to publish 8 full length articles in reputable peer-reviewed scientific journals. One of our manuscripts figure has been published on the cover page of American journal of Pathology edition. Integration of three major components of our laboratory studies, (i) Clinical

Research using tissue microarray as well as patient's clinical history, (ii) In-vitro studies using cell lines to study the functional aspects of these cancers and finally correlating these findings (iii) In-vivo using either SCID or Nude mice has greatly improved our chances in better understanding the underlying patho-physiology of cancer. This combined approach has definitely enhanced and improved the chances of treating these cancers using targeted therapy against certain genes that are being discovered with the help of these techniques.

We hope to continue with our research activities in the same fervor and enthusiasm to make 2011, even more productive than last year.

Human Cancer Genomic Research is further divided into 3 closely inter-related sections.

- Experimental Molecular Pathology
- Molecular Oncology
- Biological Repository Center

EXPERIMENTAL MOLECULAR PATHOLOGY

2010 has been the year where we have targeted a number of survival pathways that are dysregulated in various cancers that are prevalent in this region. One important pathway that we have emphasized is the FoxM1 survival pathway that has been shown to play an important role in pathogenesis of different cancers. We found in our studies that FoxM1 is found to be over-expressed in diffuse large B cell lymphoma, thyroid cancer and epithelial ovarian cancer. In addition, we also found that FoxM1 expression is associated with other proteins that render cancers to be more aggressive and lethal.

MOLECULAR ONCOLOGY

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

Utilizing the information generated by the section of experimental pathology, we target those dysregulated pathways that are playing a role in the pathogenesis of cancers. FoxM1 that has been found to be over-expressed in various cancers has been targeted using either pharmacological inhibitors or siRNA knockdown strategy. Our data shows that by inhibiting FoxM1 expression, we were able to inhibit cell growth and induce apoptosis in these cancers. We were also able to diminish the invasion/migration properties of these cancers by pharmacological intervention against FoxM1 expression. We further confirmed these findings in-vivo by inoculating tumor cells in either SCID or Nude mice and then treat them with the specific inhibitors and follow the progress of these tumors over several weeks.

BIOLOGICAL REPOSITORY CENTRE

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

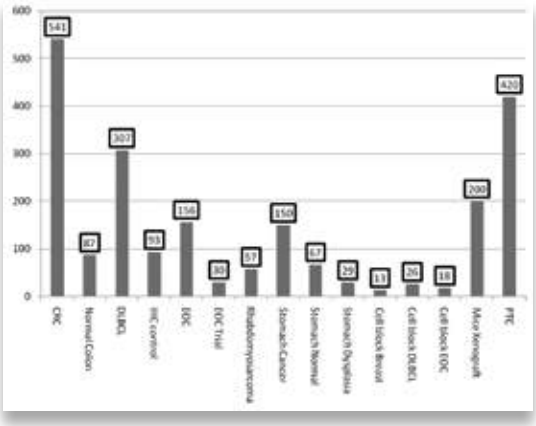
Tasks

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

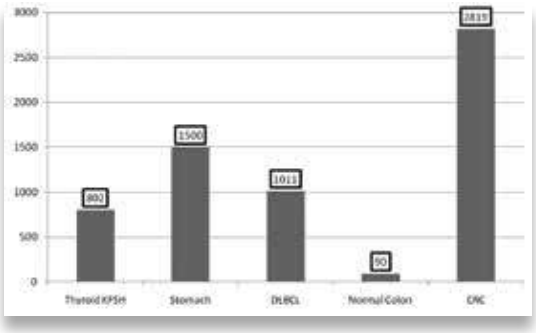
Activities

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

1. Processing biomaterial (DNA and/or RNA extraction from TMA punches of paraffin blocks) for various research projects – a total of 6222 specimens were processed in the year 2010-2011. Five to ten DNA punches obtained for each tumor specimen.



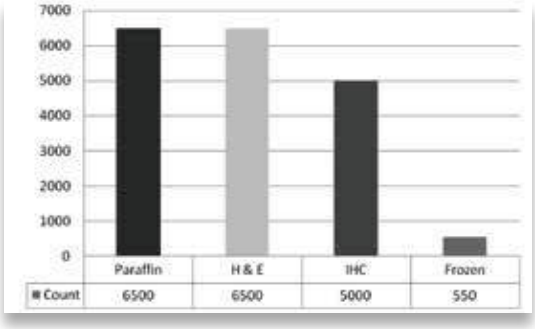
2. Cell blocks prepared from cell lines used for immunohistochemistry -57
3. Commercial cell lines acquired from ATCC and other biorepository centers expanded and grown in bulk over 700 vials frozen and stored in liquid nitrogen.
4. Processing of fresh tissue for frozen sections and formalin fixed paraffin embedded (FFPE) tissues from archival paraffin blocks for routine H&E staining and immunohistochemistry. This may include fixation, paraffin embedding, tissue cutting and section staining. Sections are cut and stained for all routine histochemical staining including hematoxylin and eosin.



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

TISSUE MICROARRAY (TMA) UNIT

Human Cancer Genomics Research has established TMA technology and has an extensive archival of tumor specimens in a TMA format. A total of 2137 tumor and normal tissue specimens were arrayed in a TMA format in year 2010-11.Six to ten TMA replicas obtained for each tumor specimens. In addition we have 3 cell line block TMA.



RESEARCH PROJECTS:

Approved Projects Funded by KACST/NCPST:

1. RAC 2080 031 - Role of c-MET in Saudi Arabian Papillary Thyroid Carcinoma for Novel Therapy.
2. RAC 2080 030 - Prognostic Significance of Genetic Alterations in Saudi Colorectal Cancers.
3. RAC 2080 029 - Cyclooxygenases: Target for Epithelial Ovarian Cancer Prevention and Treatment.

RAC Active Projects

1. RAC 2060 008 - Molecular Signatures of Diffuse Large B-cell Lymphoma (DLBCL), Lung and Ovarian Cancer: A Pilot Study.
2. RAC 2040 004 - Molecular Signatures of Cancer; Clinical Significance in Saudi Arabian and European Cancer Patients.

RAC Completed Projects

1. RAC 2070 004 - Role of PI3-kinase-AKT Pathway in Epithelial Carcinomas.
2. RAC 2040 014 - Role of JAK/STAT and PI3-Kinase Pathways in Hematological Malignancies.
3. RAC 2090 012 (SANAD Project) - Real-time PCR Assay of Terminal Deoxynucleotodyl Transferase (TdT) for detection of acute lymphoblastic-leukemia in cerebrospinal fluid.
4. RAC 2050 015 - Translational initiatives in Hematological malignancies.

Human Cancer Genomic Research is actively involved in programs relating to four different organ sites:

- Hematological Malignancies
- Thyroid
- Colon
- Ovary

HEMATOLOGICAL MALIGNANCIES

Project title

Deregulated FoxM1 Expression Mediated Signaling in Pathogenesis 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

Forkhead Box M1 (FoxM1) has been shown to play a critical role in pathogenesis of various malignancies however its role in lymphoid malignancies is not fully elucidated. Therefore, in this study, we investigated the role of FoxM1 in a large series of DLBCL tissues in a tissue micro array (TMA) format and DLBCL cell lines. FoxM1 expression was detected in 84.6% of DLBCL tumors and found to be significantly associated with early stage ($p=0.0149$), germinal centre phenotype ($p=0.0126$) and high proliferative tumor marker Ki67 ($p<0.0001$). In addition, FoxM1 expression was also significantly associated with expression of MMP-2 ($p=0.0008$), MMP-9 ($p=0.0002$), SKP-2 ($p<0.0001$) and inversely associated with p27 expression (0.0215). Our in vitro studies showed that inhibition of FoxM1 by specific inhibitor thiostrepton led to G2/M cell cycle arrest at 24 hours and inhibition of cell viability, invasion and migration of DLBCL cells and induction of apoptosis via activation of mitochondrial apoptotic pathway after 48 hours. Finally, combination of thiostrepton and Bortezomib at sub-toxic doses led to efficient apoptosis in DLBCL cells. Altogether, these results suggest that FoxM1 signaling contribute in pathogenesis of germinal centre subtype of DLBCL and may serve as useful molecular biomarker and potential therapeutic target.

Progress

Manuscript submitted to Blood, 2011.

Project title

Resveratrol suppresses constitutive activation of AKT via generation of reactive oxygen species (ROS) and induces apoptosis in diffuse large B cell lymphoma cell lines

Investigators: Khawla S. Al-Kuraya, Shahab Uddin, Azhar R Hussain, Maqbool Ahmed, Rong Bu, Saeeda O Ahmed, Zeenath Jehan, Prashant Bavi

Project description

We have recently shown that deregulation PI3-kinase/AKT survival pathway plays an important role in pathogenesis of diffuse large B cell lymphoma (DLBCL). In an attempt to identify newer therapeutic agents, we found that Resveratrol (trans-3,4', 5-trihydroxystilbene), a naturally occurring polyphenolic compound caused dose dependent inhibition of cell viability and induced apoptosis in DBCL cells. We investigated the action of Resveratrol on PI3-kinase/AKT pathway and found that Resveratrol treatment resulted in inhibition of constitutively activated AKT and its downstream targets via generation of reactive oxygen species (ROS) ultimately leading to caspase dependent apoptosis. Simultaneously, Resveratrol treatment of DLBCL cell lines also caused ROS dependent upregulation of DR5; and interestingly, co-treatment of DLBCL with sub-toxic doses of TRAIL and Resveratrol synergistically induced apoptosis via utilizing DR5, on the other hand, gene silencing of DR5 abolished this effect. Altogether, these data suggest that Resveratrol acts as a suppressor of AKT/PKB pathway leading to apoptosis via generation of ROS and at the same time primes DLBCL cells via up-regulation of DR5 to TRAIL-mediated apoptosis. These data raise the possibility that Resveratrol may have a future therapeutic role in DLBCL and possibly other malignancies with constitutive activation of the AKT/PKB pathway.

Progress

Manuscript submitted to PloS ONE, 2011.

THYROID CANCER

Project title

FoxM1 and its association with Matrix Metalloproteinase signaling pathway in papillary Thyroid Carcinoma

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

Project description

FoxM1 transcription factor has been shown to promote pathogenesis of several malignancies. FoxM1 has also been shown to be associated with Matrix metalloproteinases (MMPs) in various cancers. However, little is known about its function in papillary thyroid cancers (PTC). In this study, we investigated

the role of FoxM1 in pathogenesis of PTC using a large cohort of cancer array in a tissue micro array (TMA) format, followed by in vitro and in vivo studies using PTC cell lines and nude mice. FoxM1 was found to be over expressed in 28.4% of PTC and significantly associated with expression of MMP-9 (p=0.0004), XIAP (p=0.0024), and Bcl-Xl (p=0.0014). In vitro data using PTC cell lines showed that treatment of FoxM1 by thiostrepton resulted in inhibition of viability and induction of apoptosis. We also found that down-regulation of FoxM1 reduced the expression of MMP-2 and MMP-9 resulting in inhibition of migration and invasion in PTC cells. Finally, treatment of PTC cell line xenografts with thiostrepton resulted in growth inhibition of tumors in nude mice via downregulation of FoxM1 and MMP-2 and MMP-9. Altogether, this is the first study showing that FoxM1 deregulated signaling pathway play a critical role in the pathogenesis of PTC and may be a potential target for therapeutic intervention for treatment of these cancers.

Progress

Manuscript submitted to Oncogene, 2011.

Project title

Demethylation of TMS1 Gene Sensitizes Thyroid Cancer Cells to TRAIL Induced Apoptosis

Investigators: Khawla S. Al-Kuraya, Abdul K. Siraj, Azhar R. Hussain, Maha Al-Rasheed, Maqbool Ahmed, Prashant Bavi, Saif Al-Deen Suliman Alsobhi, Abdurahman Al-Nuaim, Shahab Uddin

Project description

Context: TMS1 is a tumor suppressor gene which encodes for a CARD (caspase recruitment domain) containing regulatory protein and has been shown to be hyper-methylated in various cancers. However, its methylation status has not been investigated in thyroid cancer. Therefore, we studied the methylation of TMS1 and its functional consequence using a panel of thyroid cell

Design: Methylation status of the promoter region of TMS1 gene was determined using methylation specific PCR in 40 papillary thyroid cancer (PTC) samples, 10 normal thyroid tissue and 7 thyroid cancer cell lines. Real time PCR and western bolt analysis was employed to assess the expression levels. 5-AZA-2'-deoxycytidine was used to demethylate thyroid cancer cell lines. Cell viability was determined by MTT assay and apoptosis was determined by using Flow cytometry.

Results: 23% of PTC samples were found to be methylated for TMS1 gene. 2 out of 7 thyroid cell lines were either completely or partially methylated for TMS1 gene resulting in loss of TMS1 expression. Treatment of methylated thyroid cancer cell lines with 5-Aza-2'-deoxycytidine resulted in demethylation of TMS1 gene leading to restoration of its expression, After demethylation, treatment of cells with TRAIL led to induction of apoptosis via activation of caspases-8, -3 and PARP. Interestingly, gene silencing of TMS1 using TMS1 specific siRNA prevented TRAIL-mediated apoptosis.

Conclusion: Our results demonstrated that TMSI gene is methylated in thyroid cancer cells and repression of methylation by 5-Aza-2'-deoxycytidine restored expression of TMS1 gene and sensitized cells to TRAIL-induced apoptosis. These findings suggest that TMS1 gene can be targeted by combination of demethylating agents with TRAIL to induce efficient apoptosis in thyroid cancer cells.

Progress

Manuscript published in Journal of Endocrinology and Metabolism, 2011

COLON

Project title

Co-expression of Activated c-Met and Death Receptor 5 predict a Better Survival in Colorectal Carcinoma

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

Project description

Dysregulated over-expression of hepatocyte growth factor and its receptor, c-Met has been reported in various cancers. However, its role in colorectal carcinoma (CRC) has not been elucidated. Therefore, we investigated the role of p-Met in Middle Eastern CRC patient samples and cell lines. p-Met was over-expressed in 80.8% of CRC and strongly associated with expression of p-AKT (p=0.0219), DR5 (p=0.0344) and Ki67 (p=0.0382) by immuno-histochemistry. Co-expression of p-Met and DR5 was seen in 52.9% CRC cases and was associated with less aggressive phenotype characterized by a histology subtype of adenocarcinomas (p=0.0083), well differentiated tumors (p=0.0003) and was an independent prognostic marker for better overall survival (p=0.0064).

PHA665752, a selective p-Met inhibitor, induced apoptosis in CRC cells via inactivation of c-Met and AKT. PHA665752 treatment also caused up-regulation of DR5 via generation of ROS and combination treatment with TRAIL and PHA665752 induced significant apoptosis. In vivo, co-treatment of CRC xenograft with PHA665752 and TRAIL significantly reduced tumor volume and weight. These data demonstrate a significant correlation between p-Met and DR5 in CRC patients. Furthermore, inhibition of p-Met signaling by PHA665752 in combination with TRAIL significantly inhibited cell growth and induced apoptosis in CRC cell lines suggesting that this may have significant clinical implications as a therapeutic target in treatment of CRC.

Progress

Manuscript submitted to American Journal of Pathology, 2011.

Project title

Genome Wide Expression Analysis of Middle Eastern Colorectal Cancer Reveals FOXM1 as a Novel Target for Cancer Therapy

Investigators: Khawla S. Al-Kuraya, Shahab Uddin, Maqbool Ahmed, Azhar Hussain, Jehad Abubaker, Nasser Al-Sanea, Alaa AbdulJabbar, Luai H. Ashari, Samar Alhomoud, Fouad Al-Dayel, Zeenath Jehan, Prashant Bavi, Abdul Khalid Siraj

Project description

In order to identify potential genes that play important role in Progression of colorectal carcinoma (CRC), we screened global gene expression using cDNA expression array on 41 CRC tissues and 25 non-cancerous colorectal tissues. Among the up-regulated genes, Forkhead Box M1 (FoxM1) has been shown to play critical role in pathogenesis of various malignancies. Using Immunohistochemistry on 448 Saudi CRC in tissue microarray format, FoxM1 overexpression was seen in 66% of CRC and significantly associated with poorly differentiated and high proliferative tumors (P = 0.0200 and 0.0018 respectively). FoxM1 expression was also significantly associated with MMP-9 expression (p = 0.0002). In vitro data using CRC cell lines showed that inhibition of FoxM1 by thiostrepton resulted in inhibition of proliferation and induction of apoptosis in a dose dependent manner. Over-expression of FoxM1 potentiated cell proliferation, cell transformation and migration/invasion of CRC cells via up-regulation of FoxM1 target genes, MMP2 and MMP9 and protected these cells from thiostrepton-mediated anti-proliferative effects. Finally, in vivo, over-expression of FoxM1 promoted growth of CRC-cell line xenograft tumors in nude mice. Altogether, our data indicate that FoxM1 signaling contribute to aggressiveness in subset of CRC and may serve as useful molecular biomarker and potential therapeutic target.

Progress

Manuscript published in American Journal of Pathology, 2011.

OVARY

Project title

Over Expression of Fatty Acid Synthase in Middle Eastern Epithelial Ovarian Carcinoma Activates AKT and its Inhibition Potentiates Cisplatin Induced Apoptosis

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

Project description

Fatty Acid Synthase (FASN), the enzyme responsible for de novo synthesis of fatty acids has been shown to be deregulated in several cancers including epithelial ovarian carcinoma (EOC). In this study, we investigated the function of FASN signalling pathway in a large series of Middle Eastern EOC patient samples, a panel of cell lines, and nude mouse model. Using immunohistochemistry, we detected over expression of FASN in 75.5% (114/151) tumor samples. Overexpression of FASN was significantly associated with tumor proliferative marker Ki-67 (p=0.0009), activated AKT (p=0.0117) and XIAP (p=0.0046). Treatment of EOC cell lines with C-75 a selective inhibitor of FASN caused inhibition of EOC cell viability via induction of apoptosis. Inhibition of FASN by C-75 led apoptosis involving the mitochondrial pathway. FASN inhibition caused down regulation of activated AKT and its down stream targets. In addition, inhibition by FASN siRNA caused downregulation of FASN and activation of caspases suggesting the role of FASN in C-75 mediated apoptosis. Furthermore, treatment of EOC cells with subtoxic doses C-75 augmented the effect of cisplatin mediated induction of apoptosis. Finally, treatment of EOC cell line xenografts with combination of C-75 and cisplatin resulted in growth inhibition of tumors in nude mice through downregulation of FASN and activation of caspases. Altogether,

our results show overexpression of FASN in Middle Eastern EOC suggesting that FASN may be a potential therapeutic target in a subset of EOC, alone or in combination with other conventional chemotherapeutic agents.

Progress

Manuscript accepted for publication in Molecular Medicine, 2011.

Project title

Aberrant FoxM1 Expression Mediated Signaling in the Pathogenesis of Epithelial Ovarian Carcinoma

Investigators: Khawla S. Al-Kuraya , Zeenath Jehan, Shahab Uddin, Maqbool Ahmed, Azhar Hussain, Thangavel Saravanan, Fouad Al-Dayel, Prashant Bavi.

Project description

FoxM1 is a member of Forkhead transcription factors with multiple biological functions. Aberrant expression of FoxM1 has been shown in many cancers however, its role has not been studied in epithelial ovarian cancer (EOC). Therefore in this study, we investigated role of FoxM1 in epithelial ovarian cancer (EOC) using a large cohort of tumor samples in a tissue microarray format, a panel of cell lines, and in a nude mouse model. Using immunohistochemistry, FoxM1 was detected in 47.4% (64/135) of the ovarian tumor samples. Overexpression of FoxM1 was also significantly associated with activated p-AKT ($p=0.0072$), Skp2 ($p=0.0121$), p-Rb ($p=0.0357$), PIK3CA p110αIHC ($p=0.0362$), XIAP ($p=0.0033$), tumor proliferative marker Ki67 ($p<0.0001$) and MMP9 ($p=0.0038$). Treatment of EOC cell lines with thiostrepton, an inhibitor of FoxM1, inhibited cell viability through induction of G2/M cell arrest, decreased expression of Skp2, cyclin D1 and consequently upregulation of p21. Furthermore, higher doses of thiostrepton treatment caused apoptosis by involving the mitochondrial pathway, through activation of caspases and down regulation of XIAP and survivin. Thiostrepton treatment also prevented cell migration and cell invasion by inhibition of VEGF and MMP2 activity. In addition, gene silencing with siRNA causes downregulation of FoxM1, and its associated downstream signaling molecules. FoxM1 inhibition causes antitumor effects in murine xenografts via downregulation of FoxM1 regulated genes. Altogether, these findings suggest that FoxM1 is dysregulated in EOC and aberrant expression of FoxM1 help in survival of EOC via modulation of cell cycle.

Progress

Manuscript submitted in Molecular Cancer Therapeutics, 2011.

COLLABORATIONS

National Collaboration

- Department of Pathology and Laboratory Medicine, KFSH&RC
- Department of Oncology Centre, KFSH&RC
- Department of Surgery, KFSH&RC
- Department of Medicine, KFSH&RC
- Department of Pediatric Hematology/Oncology, KFNCCC, KFSH&RC
- Pathology Services Division, Saudi Aramco, Saudi Arabia

International Collaboration

- Department of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

ACCOMPLISHMENTS / ACHIVEMENTS:

1. Dr. Khawla Al-Kuraya is one of the Board of Advisers of the National Geographic Al Arabiya Magazine since September 22, 2010.
2. Dr. Khawla Al-Kuraya was the First Saudi Woman who received the King Abdulaziz Award of Excellence on January 11, 2010.
3. Dr. Shahab Uddin Khan and Dr. Azhar Hussain received an Achievement Award from HRH Princess Adelah Bint Abdullah's Science and Humanitarian Award for children's cancer research on May 23, 2010.

FUTURE DIRECTION AND RESEARCH

In the coming years, we will emphasize in characterization of Saudi cancers of different origin using HiSeq Illumina to identify potential targets for therapeutic intervention. Complementing clinical research with basic scientific studies including in-vitro functional assays and in-vivo animal models will further enhance our research in the field of cancer. Determination of potential therapeutic targets will allow us to test newer pharmacological inhibitors with decreased toxicity as compared to conventional chemotherapy to improve the response to treatment. Within our research laboratory, we will continue using state-of-the-

art approaches to study fundamental questions regarding cancers in Saudi Arabia and in the Middle East. In addition to basic research, there is also a strong emphasis on translating basic science advances into more effective and highly reliable diagnostic and therapies.

PUBLICATIONS

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- Hussain AR, Uddin S, Ahmed M, Bu R, Ahmed SO, Abubaker J, Sultana M, Ajarim D, Al-Dayel F, Bavi PP, Al-Kuraya KS. Prognostic significance of XIAP expression in DLBCL and effect of its inhibition on AKT signalling. *J Pathol*. 2010 Oct;222(2):180-90.
- Uddin S, Hussain AR, Ahmed M, Al-Dayel F, Bu R, Bavi P, Al-Kuraya KS. Inhibition of c-Met is a potential therapeutic strategy for treatment of diffuse large B-cell lymphoma. *Lab Invest*. 2010 Sep;90(9):1346-56. Epub 2010 Jun 7.
- Uddin S, Bu R, Ahmed M, Hussain AR, Ajarim D, Al-Dayel F, Bavi P, Al-Kuraya KS. Leptin receptor expression and its association with PI3K/AKT signaling pathway in diffuse large B-cell lymphoma. *Leuk Lymphoma*. 2010 Jul;51(7):1305-14.
- Uddin S, Hussain AR, Ahmed M, Bu R, Ahmed S, Ajarim D, Al-Dayel F, Bavi P, Al-Kuraya KS. Inhibition of fatty acid synthase suppresses c-Met receptor kinase and induces apoptosis in diffuse large B-cell lymphoma. *Mol Cancer Ther*. 2010 May;9(5):1244-55.
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- Hussain AR, Khan AS, Ahmed OS, Ahmed M, Platanias LC, Al-Kuraya KS, Uddin S. Apigenin induces apoptosis via down-regulation of S-phase kinase protein 2-mediated induction of p27kip1 in primary effusion lymphoma cells. *Cell Prolif*. 2010;43(2):170-83.
- Uddin S, Ahmed M, Hussain A, Assad L, Al-Dayel F, Bavi P, Al-Kuraya KS, Munkarah A. Cyclooxygenase-2 inhibition inhibits PI3K/AKT kinase activity in epithelial ovarian cancer. *Int J Cancer*. 2010 Jan 15;126(2):382-94.

ABSTRACTS

- Bavi P, Ahmed M, Hussain AR, Jehan Z, Al-Sanea N, Abduljabbar A, Ashari LH, Alhomoud S, Al-Dayel F, Balde V, Uddin S, Al-Kuraya KS. Bortezomib stabilizes mitotic cyclins and prevents cell cycle Progression via inhibition of UBE2C in colorectal carcinoma. 2009 KFSH&RC Annual Research Report, April 13-14, 2010, Riyadh, Saudi Arabia.
- Uddin S , Hussain AR, Ahmed M, Al-Dayel F, Bavi P, Al-Kuraya KS. Inhibition of c-Met is a potential therapeutic strategy for treatment of diffuse large B-cell lymphoma. 2009 KFSH&RC Annual Research Report, April 13-14, 2010, Riyadh, Saudi Arabia.
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- Siraj AK, Al-Rasheed M, Hussain AR, Bavi P, Al Nuaim A, Al-Dayel F, Uddin S, Al-Kuraya K. TMS1 gene promoter methylation confers resistance to papillary thyroid carcinoma cell lines. 2009 KFSH&RC Annual Research Report, April 13-14, 2010, Riyadh, Saudi Arabia.
- Uddin S, Ahmed M, Hussain AR, Jehan Z, Al-Dayel F, Munkarah A, Bavi P, Al-Kuraya KS. Bortezomib-mediated expression of p27Kip1 through S-phase Kinase Protein 2 degradation in epithelial ovarian cancer. 2009 KFSH&RC Annual Research Report, April 13-14, 2010, Riyadh, Saudi Arabia.
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potential clinical implication. 5th International APOCP Conference, April 3-7, 2010, Istanbul, Turkey.

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- Siraj Ak, Al-Rasheed M, Hussain A, Bavi P, Al-Nuaim A, Al-Dayel F, Uddin S, Al-Kuraya K. TMSI Gene Promoter Methylation confers resistance to papillary thyroid carcinoma cell lines. Advances in Cancer Research: From the Laboratory to the Clinic, March 07-10, 2010, Dead Sea, Jordan.
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THE

Stem Cell Therapy Program

The Stem Cell Therapy Program

Director

Chaker N. Adra, PhD

Administrative Support Staff

Madeline Fiji Schuck - Ranera

Maria Linda Rasing -Macasieb

The "Stem Cell Therapy Program" focuses on investigating the molecular and cellular mechanisms of stem cell biology and their application for therapeutic use in a number of clinical areas including spinal cord injuries, cardiovascular, neurodegenerative, renal, liver and autoimmune diseases, diabetes and cancer. The department is working towards achieving the goal of excellence in stem cell research and therapy in the Middle East and worldwide. Members of the program are actively participating in basic, pre-clinical and translational clinical research, teaching, and in collaborative projects with the scientific and clinical community. In addition, this program is in dynamic collaboration with the Imperial College London and members of the Harvard Medical School and its affiliated Hospitals, in particular, The Transplantation Center, and The Renal Divisions at The Brigham and Women's Hospital and Children's Hospital Boston, and The Massachusetts General Hospital, The Dana-Farber Cancer Institute, and The Massachusetts Institute of Technology (MIT), United States of America. We are convinced that a well-funded team of scientists with expertise in tissue engineering, stem cell biology and transplantation will bring the dream of curing human disease by implanting fabricated organs to reality. We are moving the field forward tremendously and this have led to our conviction that the generation of living constructs for human therapy, including whole organs such as a heart, liver, pancreas, lung and kidney, is close at hand and will happen at the KFSHRC. KFSHRC is recruiting now the best Saudi biologists, engineers, and clinicians in the world and we firmly believe that a coordinated Program that brings all these talents together will achieve our ultimate goal - the fabrication of vital organs through bioengineering. Achieving this goal will change medicine as we know it. Importantly, the program is committed to training, recruiting and advancement of Saudi scientists, technicians and students.

LIST OF SIGNIFICANT AND SCIENTIFIC ACHIEVEMENTS

- Established an independent unit to study stem cell biology in collaboration with The Transplantation Center at Harvard Medical School.
- Established scientific collaborations with multiple institutions both national and international with combined scientific and experimental efforts towards achieving the goal of excellence in stem cell research in the Middle East area and worldwide.
- Thirty One (31) published Abstracts, twelve (12) publications, and several manuscripts in preparation.
- Twenty Nine (29) RAC Approved Research Projects under the Stem Cell Therapy Program, Research Centre.
- Three (3) Projects were approved for funding by KACST and the National Comprehensive Plan for Science and Technology (NCPST);
  1. Investigating the Immunogenicity of Breast Cancer Stem Cells (ARP #24-29/RAC# 2080 045).
  2. Identification and Therapeutic Targeting of ABCB5+ Tumor Stem Cells (MED #483-20/RAC# 2080 023)
  3. Stem Cells Interactions with the Inflammatory Environment in Multiple Sclerosis and other Neurodegenerative Diseases of the Central Nervous System (MED #494-20/RAC # 2070 018)
- Launched the 1st Clinical Trial entitled: Stem Cell Therapy in Patients with Severe Peripheral Arterial Disease of the Lower Limbs.
- The Asthma/Atopy Project was launched in collaboration with Dr. Bandar Al-Saud as Principal Investigator (PI).
- Potential Identification of new HLA alleles specific for the Saudi population, pending verification.
- Identification of HLA Alleles in Normal Saudi Individuals by Sequence Based Typing.
- Correlation of Saudi population associated HLA genes and certain autoimmune diseases progression and transplant outcome.
- Generating powerful DC which may lead to national immune therapeutic modulate for CML patients based on Saudi genome.
- The Saudi Kidney Health Program towards Kidney Bio-Engineering and Transplant was launched and affected families have been successfully recruited.
- Established the foundation of The Saudi HLA Genome Database to advance the fields of hematopoietic stem cell transplantation and kidney transplantation in the Kingdom of Saudi Arabia.
- International Patents on major scientific discoveries for diagnostics and patient care have been issued to King Faisal Specialist Hospital and Research Centre, Riyadh, Kingdom of Saudi Arabia
- A "Silver Award", for Excellent Research from King Abdul-Aziz City for Science and Technology (KACST) was received by Dr. Khalid Hussein, Senior Scientist at Stem Cell Therapy Program.
- Established successful collaboration with national and international institutions on both research projects and education programs such as; The Harvard Medical School Fellowships (4 Awards: $75,000 per year for a period of 3 years), Massachusetts College of Pharmacy (MCPAHS), Boston, MA. USA (1 Pharm D), 5 PhD Students in UK, In-House Training (Saudi Students and Employees). Regular training of technical staff abroad, attending professional meetings to present research work at international and national scientific meetings/conferences.
- Development of staff expertise through our departmental continuing education program; Conducted courses and workshops including (1) First and Second Introductory Course & Proteomics Workshop, Oct. 2009 - 2010 (2) Kidney Diseases, Fall 2012 and (3) Stem Cell and Organ Bio-Engineering Think-Tank in preparation.
- Host "Summer Training Program" for Alfaisal University Medical Students.
- Host "Summer Training Program" for Gifted Students from Ibin Sina program for future scientists.
- The Stem Cell Therapy Program runs quality research laboratories towards achieving excellence in the field of stem cell research, repair of birth defects and organ bio-engineering for transplantation.

SIGNED MEMORANDA OF UNDERSTANDING:

1. KFSH&RC and INSERM and University Hospital Center (France), 4th of November 2007.
2. KFSH&RC and The Harvard Medical School (USA), 19th of January 2008.
3. KFSH&RC and The Transplantation Research Center at Harvard, January 2008.
4. KFSH&RC- PSCDR- Swiss Stem Cell Bank, Founders Council Ceremony, Jeddah, Saudi Arabia, 09 September 2008.

5. KFSH&RC and Karolinska University Hospital and Lund University, Sweden (Established collaborative project since 2009).

COLLABORATORS

International

- Massachusetts General Hospital, USA.
- Brigham and Women's Hospital, Boston, MA, USA.
- Children's Hospital Boston , MA, USA.
- Harvard Medical School, USA.
- Harvard University, USA.
- Massachusetts Institute of Technology (MIT), USA.
- Karolinska Hospital and Institute, Stockholm, Sweden
- Lund University, Lund, Sweden
- Dubai Harvard Foundation for Medical Research, Dubai, UAE
- Imperial College, United Kingdom.
- Dr. Tilanus, Head Molecular Lab at Utrecht University, Netherlands to utilize high-resolution method for HLA typing.
- Prof Derek Middleton, Northern Ireland Histocompatibility & Immunogenetics Laboratory, Belfast, Northern Ireland for allele frequencies.

National

- Department of Pathology & Laboratory Medicine, KFSH&RC, Riyadh, KSA (Tissue and Stem Cell Banking for Solid Tumors, and Identification and Therapeutic Targeting of Cancer Stem Cells).
- Department of Urology, KFSH&RC, Riyadh, KSA (Discovering Biomarkers for Prostate Cancer – just published results in International Journal Oncology, Jan 2011).
- Department of Medicine, KFSH&RC, Riyadh, KSA (Discovering Markers for Classification of Lupus Nephritis)
- Renal Transplant Program, KFSH&RC, Riyadh, KSA (Discovering Markers for Organ Transplant/Rejection).
- Cord Blood Bank, Department of Pathology and Laboratory Medicine, KFSH&RC, Riyadh, KSA.
- Department of Pediatrics, KFSH&RC, Riyadh, KSA (Discovering Markers for Polycystic Kidney Disease).
- Department of Neurosciences, KFSH&RC, Riyadh, KSA (Developing Stem Cell Banking and Discovering Markers for Brain Tumors).
- Oncology Centre, KFSH&RC, Riyadh, KSA (Discovering Treatment Response Markers for Cancer Patients).
- Department of Surgery, KFSH&RC, Riyadh, KSA (Developing Stem Cell Banking and Discovering Markers for Breast, Colorectal, and Cancers and other Solid Tumors).
- Prince Fahad bin Salman Charity Association for Renal Failure Patients Care, Riyadh, KSA.
- Failure Patients Care, Riyadh (Initiated Kidney Health Research).
- Prince Salman Centre for Disability & Research, Riyadh, KSA.
- King Saud University, Riyadh, KSA (Research on Neurodegenerative Disease).
- Prince Fahad bin Salman Charity Association for Renal Failure Patients Care, Riyadh, KSA (Initiated Kidney Health Research).
- DNA Cell Cycle Repair.

PATENTS ISSUED

- Inventor: Chaker N. Adra. Lysosomal-associated multispanning membrane protein, LAPTM5 and nucleic acid encoding LAPTM5. 6,153,403. 2000 Nov 28
- Inventor: Chaker N. Adra. HT.sub.m4 methods of treatment and assays, agonists and antagonists. 5,972,688. 1999 Oct 26
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- Inventor: Chaker N. Adra. Recombinant HT.sub.m4 gene, protein and assays. 5,552,312. 1996 Sep 3
- Inventor: Chaker N. Adra. Method for detecting a predisposition to asthma and atopy. US2003165992. 2003 Sep 4
- Inventor: Chaker N. Adra. Methods and Compositions for Cell Cycle Regulation. Application Number US11779381. Publication date 06/26/2008 U.S
- Inventor: Chaker N. Adra. HTm4 Used For Cell Cycle Regulation through Its Interaction with Kap Application Number US2006001844. Publication date 07/19/2007
- Inventor: Chaker N. Adra. Granulocyte Subtype Selective Receptors and Ion Channels and Uses Thereof. Application Number US5007519. Publication date 10/13/2005RAC

APPROVED RESEARCH ACTIVITIES:

Project title

Development of Autologous Stem Cell Therapy for Patients with Severe Peripheral Arterial Disease of the Lower Limbs-A Phase II Non-Randomized Study, RAC # 2081 021.

Principal Investigator: Dr. Chaker Adra

Co-Principal Investigators: Dr. Nahar Al-Anezi and Dr. Hind Al-Humaidan

Co-Investigators: Dr. Saleh Al-Othman, Dr. Ayodele Alaiya Dr. Fouad Hassan Al-Dayel, Dr. Tauqir Ahmed Rana, Dr. Morad Al-Kaff, Dr. Tarek Al-Owaidah and Dr. Bassel Safi

Advisors: Dr. Mohamed H. Sayegh and Dr. Michael S. Conte

Project description

The primary aim of this study is to use autologous transplantation of mononuclear stem cells (MNCs) derived from either bone marrow (BM) or peripheral blood from patients with severe Critical Limb Ischemia (CLI) and to assess the efficacy, safety and feasibility of treatment protocol. The study in addition; aims to identify Peripheral Arterial Disease (PAD)–associated biomarkers using global protein expression analysis.

Methods

Twenty patients diagnosed with CLI; that are not amenable to any intervention or bypass-able patients with high risk for surgery will be recruited for the study. MNCs will be sorted in the lab either from harvested iliac crest BM or from peripheral blood. MNCs will then be injected either intramuscular alone in the calf of the ischemic leg or in combination with intra-arterial injection via the femoral artery of the ischemic leg. Patients will be assessed for 3 to 12 months post transplantation to the outcome of the treatment.

We will also use proteomics approaches to identify potential biomarkers from tissue biopsies and blood samples that could be useful in the development of Stem Cells for therapeutic strategies in regenerative disorders and arterial occlusive diseases.

Significance

The outcome of this clinical trial will improve our understanding of the potential use of Stem Cell therapy as an alternative intervention for patients with severe PAD. In addition, association between results from bench-work with results obtained in the clinical trial will further assist the identification of cellular and molecular PAD-associated biomarkers, towards improving diagnosis of PAD and developing better treatment strategies.

Progress/ Major Findings

1. The first progress report was submitted
2. Only two patients have been recruited and injected with stem cells, but the patients were lost to follow up.
3. We are making efforts to involve other satellite hospitals with in and outside Riyadh to refer patients who meet the study inclusion criteria. It is anticipated that number of patient recruitment will be improved to allow meaningful evaluation of treatment protocol.

Project title

Expansion and Differentiation of Human Embryonic and Hematopoietic Stem Cells Using Proteomics: The Therapeutic Use of Stem Cells in Disability Research, RAC #2080 050 (ARP 29-95).

Principal Investigator: Dr. Chaker Adra

Co-Investigators: Dr. Hind Al-Humaidan, Dr. Ayodele Alaiya, Dr. Andrew Wetzig, Dr. Maha Al-Mozaini, Dr. Saleh Al-Othman, Mr. Pulicat S. Manogaran and Dr. Hazem Ghebeh

Project description

A primary goal of this work is to find new ways to identify stem cells and discover what sort of media they need for growth in vitro and how to differentiate them reproducibly into variable specific cell lineages. We will look at how different molecules changes using high-throughput proteomics to map the cellular protein profile and the secreted proteins in the culture media to develop standardized protocols for reproducible tissue engineering. We are also going to label these proteins with fluorescent dyes and compare the protein profile of the starting material with the cultured cells (this is called differential two dimensional gel electrophoresis, DIGE) and use this to follow changes in stem cells as they grow and differentiate and give an intelligent feed-back system of how protein regulation is changing as the culturing conditions are varied.

This is a collaborative research project between the Proteomics Facility of the Stem Cell Therapy Program at KFSH&RC, Riyadh, Saudi Arabia and the Proteomics Facility at Imperial College, London with a major aim to help the growing number of individuals suffering from disability in Saudi Arabia. Integration of proteomic studies carried out at the two complementary proteomics centers will serve the purpose of stem cell characterization for clinical applications.

Progress

Our preliminary 2-DE DIGE separation of umbilical cord stem cells was done with satisfactory resolution.

We plan to carry out the same type of analysis using discarded samples from the IVF clinic.

Project title

Investigating the Immunogenicity of Breast Cancer Stem Cells, RAC # 2080 045 (Funded: ARP 24-29).

Principal investigators: Dr. Chaker Adra and Dr. Hazem Ghebeh

Co-Investigators: Dr. Monther Al-Alwan, Dr. Taher Al-Tweigeri, Dr. Khalid Al-Faqeeh and Ghida Sleiman

Project Description, Progress, Major Findings

There is accumulating evidence that cancer is originated and sustained by cells called "cancer stem cells (CSC)". These cells share many characteristics of the normal stem cells including the self-renewing ability. Thus, it is possible that they also have the immune privilege properties of normal stem cells.

This proposal studies how cancer stem cells effect antigen presentation and immune response generation. It also investigates the role of CSC in the creation of immune suppressive microenvironment, which finally leads to tumor escape from the immune system surveillance.

The first step was to identifying the population of breast cells that contains the stem cells. Up to date, there are conflicting results in the literature on the phenotype of normal breast stem cells. They are described as Ep-CAMhigh, CD49f+ cells by some groups (Villadsen et al 2007) while they are described as Ep-CAM low CD49f+ cells by others (Eirew et al 2009). On the other hand breast cancer cells are described as CD44high/CD24low or ALDH+ cells.

Single cells analyzed with Fluorescence Assisted Cell Sorting (FACS) were labeled with antibodies against EpCAM, which typically labels luminal cells of the breast ducts and lobules, and CD49f, which label the basal layer of the ducts and lobules. The two antibodies gave four populations of cells as indicated in Figure1. Both Ep-CAMhigh CD49f+ and EpCAMlow CD49f+ cells produced mammospheres when cultured in altra low attachment medium indicating their stem-like ability.

The next step is to identify the stem-like cells among these two groups of cells with higher purity and then study their immunogenecity.

Project title

Genetic Basis of Kidney Disease in the Kingdom of Saudi Arabia, RAC # 2080 042.

Principal Investigators: Dr. Chaker Adra and Dr. Martin Pollak

Co-Investigators: Dr. Khaldoun Al-Romaih, Dr. Hamad Al-Mojalli, Dr. Hadeel Al-Manea, Dr. Ayodele Alaiya, Dr. Hind Al-Humaidan, Dr. Mamdouh Al-Baqumi, Noura Atallah and Alia Iqniebi

Project description

The focus of this collaborative research is on kidney nephropathies, with a particular interest in the study of the genetics, and epigenetics of renal diseases and the potential application of stem cells for novel therapies. In the first project in this collaborative effort we are recruiting families with kidney disease to determine if defects in known genes can account for the disease by analysis of DNA sequence and to explore the possibility of identifying novel disease causing mutations/genes. In families in which multiple members share the same kidney disease, we are using genetic linkage analysis to identify chromosomal regions that are associated with the disease inheritance. We will then identify the specific DNA change within these regions. In addition expression proteomics will be conducted towards discovery biomarkers for accurate typing and classification of kidney diseases.

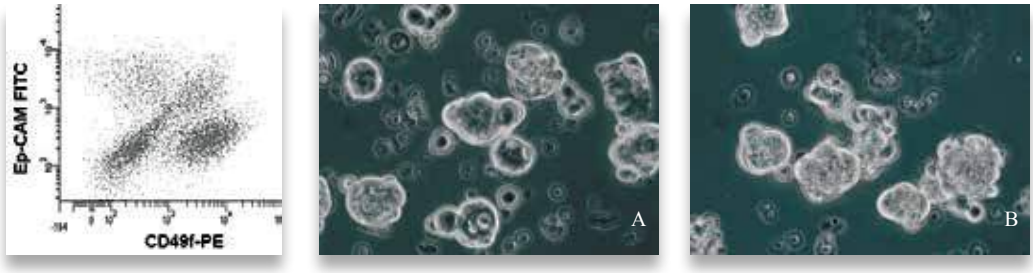

Figure 1. Both Ep-CAM^{high} /CD49f+and Ep-CAM^{low} /CD49f+ sorted by flow cytometry (A) were able to produce mammospheres when cultured on ultra-low attachment surface as shown in (B).

Progress

1. **Identification and recruitment of subjects with FSGS:** In the past 10 months we ascertained FSGS families and sporadic FSGS patients. We extended each family maximally. This required characterizing not only individuals with FSGS, but also analyzing the phenotype of other family members by assessing urine protein excretion, serum creatinine, and standard urinalysis. We ascertained families based on the criteria listed in the methods of the original proposal, in brief, at least one family member have biopsy documented FSGS which appeared to be primary rather than secondary, and other family members are considered to be affected if they have urine microalbumin/ creatinine ratio of greater than or equal to 300 mg/g creatinine on repeated measurements, indeterminate if urine microalbumin is between 30 and 300 mg/g creatinine and unaffected if < 30 mg/g. We obtained blood samples from consented participants and DNA extraction was performed on all samples. Urine also was obtained for protein measurement in family members with no signs of the disease to confirm their phenotype. We will continue to actively ascertain more families through an established network of nephrologists and renal pathologists throughout Saudi Arabia.
2. **Mutational analysis of known FSGS genes in the sample set:** The number of disease causing mutations identified in the ACTN4, TRPC6, and CD2AP genes is relatively small. Identifying additional mutations that cause human disease is important both for understanding the genetic basis of FSGS as well as for understanding structure-function relationships within the encoded proteins. We performed mutational screen of a number of known FSGS genes including ACTN4, NPHS2, and TRPC6 in patients with FSGS and we Continue determination of FSGS-associated variants in these known genes as this is essential both for understanding the biology of this disease as well as structure/function and genotype/phenotype relationships. We will resequence FSGS genes in probands from new FSGS families and subjects with sporadic FSGS as they are recruited into these studies by our collaborating physicians.
3. **Genetic linkage analysis to identify new disease loci:** We performed genome-wide linkage analysis in potentially genetically informative families. We used Affymetrix SNP chips for this purpose (Mapping 250K Nsp from Affymetrix), as they are a relatively cost-effective method for complete genome coverage in addition to being genetically highly informative. We used standard statistical methods as implemented by widely used software programs (see original proposal for details) for evaluation of genetic linkage. Heterozygosity and Homozygosity mapping methods were applied to identify loci responsible for disease under assumptions that disease is dominant or recessive. Our method relies on the identification of genetic regions identical-by-descent on both alleles from a common ancestor. We are identifying candidate genes in linked regions on the basis of 1) Expression in podocyte and/or glomerulus 2) Proximity to a known FSGS/NS gene in protein interaction network 3) Other compelling data suggesting a gene is a strong candidate. Although initially we purposed that the Mutational analysis of candidate genes will likely take place beyond the initial two year period of this project, we have already started the sequencing of candidate genes from linked regions at the time of writing this project update.

In collaboration with consultants from the Pediatrics and Pathology departments at the KFSH&RC and scientists from Harvard, Boston, the project was launched on January 2009 and 20 families were enlisted. 28 individuals from 8 families were already recruited and DNA, RNA and serum was extracted from the blood samples of these individuals. The team continues to ascertain families with kidney disease and, more importantly, to extend the number of participants from the families already enlisted in order to increase the power of genotyping/linkage analysis that we intend to perform. Primers for a number of genes that are known to cause kidney nephropathies have been designed (including primers for ACTN4, NPHS1, NPHS2, and TRPC6) and DNA amplification followed by sequencing is ongoing. The project was also the basis on which collaboration was initiated between Dr. Chaker Adra (Director, SCTP-RC) and Dr. Martin Pollak at the Renal Divisions of the Brigham and Women's Hospital BWH-Harvard Institutes of Medicine in Boston, USA. In addition Dr. Adra supported a Scholar Researcher –Fellowship position at BWH-Harvard for a Saudi Arabian postdoctoral fellow from the SCTP in the aim of conducting some of the work described in the project in one of the leading labs in Kidney Failure diseases in the world (Dr. Pollak's lab, BWH-Harvard).

4. **Renal Proteomics analysis:**
   Proteomic Analysis of FSGS and Lupus Nephritis has been conducted and a number of proteins were differentially expressed and will be validated as renal biomarkers: A manuscript on Lupus Nephritis class IV Global Versus Segmental has recently been submitted to the Journal of the American Society of Nephrology, April 2011).

Project title

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

Principal Investigators: Dr. Bandar Al-Saud and

Co-Principal Investigator: Dr. Chaker Adra

Co-Investigators: Dr. Ayodele Alaiya, Dr. Monther Al-Alwan, Dr. Hind Al-Humaidan, Dr. Ameera Gaafar and Dr. Alia Iqniebi

Project description

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

Progress and Major Findings

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

Project title

Identification and Therapeutic Targeting of ABCB5+ Tumor Stem Cells, RAC #2080 023 (Funded: MED 483-20).

Principal Investigator: Dr. Chaker Adra

Co-Investigators: Dr. Dahish Ajarim, Dr. Hind Al-Humaidan, Dr. Fouad Hassan Al-Dayel, Dr. Ayodele Alaiya, Dr. Asma Tulbah, Dr. Tarek Amin, Dr. Imaduddin Kanaan, Dr. Hazem Ghebeh and , Dr. Khaled Al-Faqeeh

Project description

ATP binding Cassette B5 (ABCB5) is an energy-dependent drug efflux pump for the fluorescent probe rhodamine and to drugs like doxorubicin. This transporter is abundantly expressed by normal melanocytes, and it has been found to identify the small population of cancer stem cells in melanoma. Very little is known about the expression of this molecule in normal and malignant breast.

Using flow cytometry we studied the expression of this molecule in normal breast and in breast cancer cells. Results show that ABCB5 is expressed in the epithelial as well as the mesenchymal cells of the breast. Among the epithelial cells, the expression is mainly in the myoepithelial cells as evidenced by the co-expression of CD10, CD90 and CD49f (Figure 2).

In addition to the myoepithelial cells, ABCB5 is expressed on stem-like cells of the breast as shown mammosphere formation assay, which measures the cells' ability to grow without adherence to the culture substratum. ABCB5 positive cells were able to form mammospheres significantly more than their negative counterparts (Figure 3).

Breast cancer cell lines like MDA-MB-468 and MCF-7 expressed ABCB5 on the cell surface (Figure 4). Our findings so far suggest that ABCB5 expression is associated with cells that have stem cell/progenitor phenotype in a fashion similar to the skin and encourage for further studies to examine its importance in breast cancer and other types of tumors.

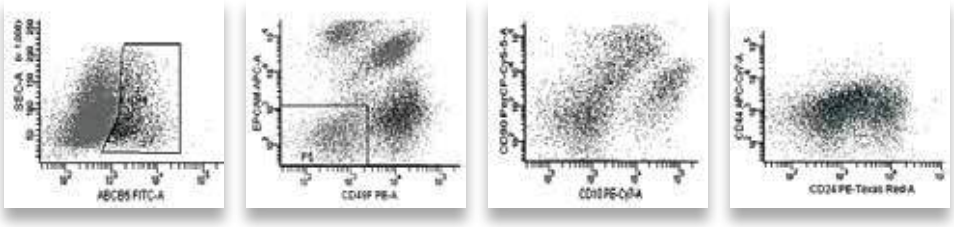

Figure 2. ABCB5 is expressed in the myoepithelial cells of the breast.

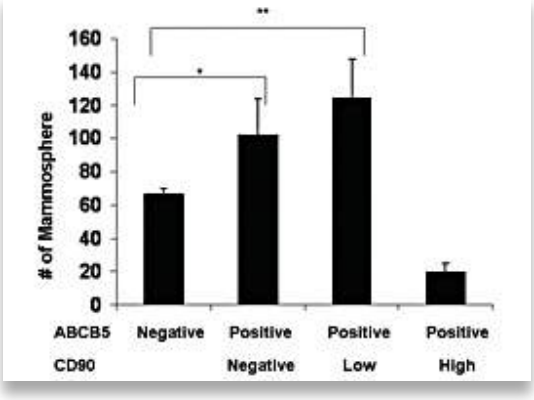

Figure 3. ABCB5 positive cells form mammospheres significantly more than their negative counterparts. * shows significance (p< 0.05), ** shows high significance (p< 0.001).

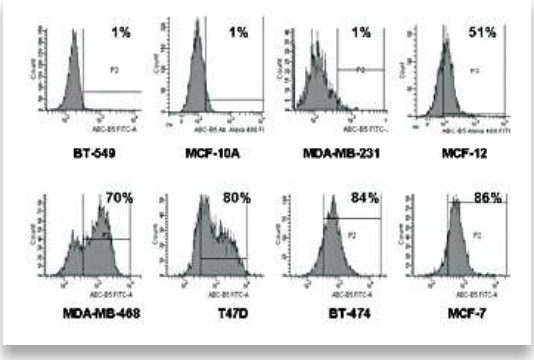

Figure 4. ABCB5 is expressed on some breast cell lines while it is negative for others.

Project title

Proteomic Analysis of Human Breast Cancer Stem/ Progenitor Cells, RAC # 2080 021, (Proteomics)

Principal Investigators: Dr. Ayodele Alaiya and Dr. Chaker Adra

Co-Investigators: Dr. Fouad Al-Dayel, Dr. Hind Al-Humaidan, Dr. Dilek Colak, Dr. Ghebeh Hazem, Dr. Asma Tulba, Dr. Taher Al-Tweigeri and Prof. Godovac-Zimmermann J.

Project description

The goal of this study is to investigate the critical molecular alterations affecting breast cancer stem cells, and how they interact with their microenvironment. The phenotypic characteristics of mammary stem cells will be defined at the protein level using a proteomics approach. This will provide information which could be used to improve both the diagnosis of breast cancers and the ability to predict clinical outcomes and response to the current treatment modalities. Furthermore, new selective therapeutic strategies could be developed targeting breast cancer stem cells while sparing normal stem cells.

This is a PhD student's project in collaboration with University College London.

Progress and Major Findings

1. Breast cancer tissue samples have been obtained from 6 patients.
2. All collected samples, so far, have been processed for isolation of epithelial cells.
3. Dissociated cell culture was attempted on one sample and protocol optimization is ongoing.
4. Sorting of the tissue mammary epithelial cells is being optimized.
5. The cell extraction method for the isolation of stem cells is currently being optimized.
6. The cell extraction method and optimization for proteomics analysis is ongoing.
7. This is a priority project focusing on identification of stem cell biomarkers at protein level.
8. An abstract and poster presentations at HUPO World Congress, Sydney Sept 2010.

Project title

The Propagation of Mesenchymal and Neural Stem Cells from Adult Olfactory Mucosa, RAC # 2080 007

Principal Investigator: Dr. Chaker Adra

Co-Investigators: Dr. Ayodele Alaiya, Dr. Andrew Wetzig, Dr. Hind Al-Humaidan, Dr. Imaduddin Kanaan and Dr. Monther Al-Alwan

Project description

The overall aim of this project is to develop a therapeutic adult stem cell treatment for spinal cord injuries. Both mesenchymal and neural stem cells could be harvested from the patient's olfactory mucosa and used together to treat the injured spine. In this way the immunosuppressive and neurotrophic properties of mesenchymal stem cells (MSCs) would be combined with the ability of neural stem cells to differentiate into replacement neurons. The aims of this project are to 1)

determine the presence of MSCs in the olfactory mucosa, 2) compare olfactory MSCs with MSCs derived from the bone marrow and breast fat, known sources of MSCs.

Progress

1. Olfactory mucosa cells demonstrated a similar phenotype to both bone marrow and breast fat cells – known sources of mesenchymal stem cells.
2. Olfactory mucosa cultures demonstrated a higher (approximately double) colony forming efficiency than both bone marrow and breast fat cells.
3. Olfactory mucosa cultures contained few cells that are able to function as mesenchymal stem cells as evidenced by the rare adipocyte and osteocyte differentiation events and the lack of chondrocyte differentiation observed.
4. Olfactory mucosa cells, along with breast fat and bone marrow cells express high levels of fibroblast associated markers.
5. We are the first to demonstrate that putative mesenchymal stem cells can be enriched from non bone marrow tissue, in this case olfactory mucosa, by selecting the CD90 negative population.
6. Both bone marrow and breast fat cells function as mesenchymal stem cells, as evidenced by osteocyte, adipocyte and chondrocyte differentiation. Phenotypic analysis however, demonstrated some key differences between the two cell populations suggesting there may be tissue specific differences between mesenchymal stem cells.

Project title

Neurosteroids and Alzheimer's Disease: Protection against Beta-Amyloid Peptide-Induced Toxicity in Neuronal Cells, RAC # 2080 005

Principal Investigator: Dr. Fadia El-Bitar

Co-Investigators: Dr. Chaker Adra and Dr. Yvette Akwa

Project description

Alzheimer's disease is the most common cause of dementia in the elderly. The toxicity of β-amyloid (Aβ) peptides is thought to be involved in neuronal damage in this pathology. Our work is based on the use of natural pregnenolone sulfate (PREGS) which is one of the major neuroactive steroids produced in the central nervous system.

Our main objective is to investigate in vitro if PREGS has neuroprotective activity against Aβ peptide-induced neurotoxicity, using rat neuroblastoma B104 as cell culture model.

Progress / Findings:

We previously demonstrated (annual report of 2008) neuroprotective properties of PREGS against fibrillary form of human fAβ1-42 neurotoxicity. In the present work, we are examining the capacity of PREGS to correct soluble form of human sAβ25-35 neurotoxicity because this peptide fragment posses the most efficient toxic core related to Aβ1-42 peptide.

To achieve this goal, we showed the following:

1. The neurotoxicity of the soluble form of human sAβ25-35 peptide started to be induced on B104 cells at 5μM after 6h treatment compared to control cells.
2. Most importantly, we demonstrated that PREGS was able to provide neuroprotection against sAβ25-35 neurotoxicity.
3. Thus, our results revealed neuroprotective activity of PREGS against both forms of peptides: fAβ1-42 and sAβ25-35.

Overall, treatment with a specific neuroactive steroid such as PREGS that counteracts the neurotoxic effects of Aβ peptide may be promising against neurodegeneration in Alzheimer's Disease.

Project title

Stem Cells Interactions with the Inflammatory Environment in Multiple Sclerosis and other Neurodegenerative Diseases of the Central Nervous System, RAC # 2070 018 (MED 494-20)

Principal Investigator: Dr. Chaker Adra

Co-Investigators: Dr. Ayodele Alaiya, Dr. Imaduddin Kanaan, Dr. Samia Khoury, Dr. Joel Stern, Weassim Elyaman, Dr. Thamer AlKhairallah, Dr. Monther Al-Alwan and Kholoud Al-Saud (PhD Candidate)

Aims of the study

1. To examine the effect of Interferon (IFN)-gamma and the transcription factor STAT1 on the self-renewal program of Neural Stem Cells (NSCs) *in vivo* and on their molecular program *in vitro*.
2. To examine the effect of IFN-gamma on the migration of NSCs *in vivo* and on their molecular program *in vitro*.
3. To examine the effect of STATI on the differentiation of NSCs *in vivo* and on their molecular program *in vitro*.

Methods

Several animal models will be used to determine the effect of STAT1 deficiency in NSCs in an inflammatory environment. This includes the use of STAT1 knockout mice and adaptive transfer of GFP-labeled STAT1-KO NSCs into wild type mice with Experimental Autoimmune Encephalomyelitis. To determine the effect of Interferon-gamma on NSCs migration in vivo in an inflammatory environment, IFN-gamma-KO GFP-labeled NSC will be adaptively transferred to wild type mice. Samples will also be subjected to proteome analysis using 2-DE, protein chips and mass spectrometry. Using these methods, the effect of STAT-1 and IFN-gamma genes on NSCs self-renewal capacity and migration will be assessed.

Significance

Human embryonic stem cells represent great hope for successful treatment of diseases in the future including; Multiple Sclerosis, Alzheimer's Disease, Parkinson's Disease, Spinal Cord Injuries, Diabetes and Cardiovascular Disease. There is particular interest in using stem cells in the treatment of neurological disorders, because these injures are permanent due to the irreversibility of neuronal damage. In light of the lack of treatment for Multiple Sclerosis, the promise of stem cell therapy offers great hope in tissue repair, replacement and regeneration that will lead to new clinical innovations and revolutionize Personalized Medicare.

Progress/ Major Findings

1. The project was awarded KACST funding (#08-MED494-20)
2. The animal experiments have commenced.

Project title

Proteomics Approach to Biomarker Discovery in Aplastic Anemia, RAC #2060 021.

Principal Investigators: Dr. Ayodele Abdulkareem Alaiya and Dr. Mahmoud Al-Jurf

Co-Principal Investigators: Dr. Naeem Chaudhri and Dr. Hazzaa Al Zahrani

Co-Investigators: Dr. Mai Al-Mohanna, Dr. Entezam Sahovic, Dr. Fahad Al Mohareb, Dr. Fahad AL Sharif, Dr. Hamad Al Omar and Dr. Ali Al Shanqeeti

Project description

We will analyze global protein expression profiles in patients with aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH) and hypoplastic myelodysplastic syndrome (MDS). The goal is to identify novel protein biomarkers that can differentially diagnose various bone marrow failure syndromes and provide accurate patient stratification for treatment.

Progress

1. 24 samples has been collected and partly analyzed (AA=10 MDS=5 PNH=3, NBM=1, 3 =pending pathology report. Sample processing/optimization have been completed.
2. Our preliminary results show that the three-disease entities shares very similar protein fingerprints.
3. We are in the process of conducting peptide mass fingerprinting by MALDI-TOF-MS and /or de novo sequencing (LC/MS/MS) for the identification of the differentially expressed proteins

Project title

Investigating the role of the actin bundling protein (fascin) in regulating dendritic cell migration and breast cancer metastasis in Saudi population, RAC # 2060 016.

Principal Investigator: Dr. Monther Al-Alwan

Co-Investigators: Dr. Hazem Ghebeh, Dr. Asma Tulbah, Dr. Taher Tweigeri, Dr. Dahish Ajarim and Dr. Mahmoud Al Jurf

Project description

The cytoskeleton has been reported to regulate cell's morphology and motility. The actin-bundling protein, fascin, is a member of the cytoskeletal protein family. While it has restricted expression in specialized normal cells, many studies have reported fascin expression in various transformed cells including breast cancer. The exact role of fascin in breast cancer cells has not been fully understood. The main aim of this proposal is to examine whether fascin induction in breast cancer facilitates metastasis and delineates the underlying mechanism.

Progress / Major Findings

1. An abstract was published at the HUPO World Congress, 19-23 Sept 2010 Sydney, Australia. Monther Al-Alwan, Safiah Olabi1, Hazem Ghebeh, Eman Barhoush, Asma Tulbah, Taher Tweigeri, Dahish Ajarim, Ayodele Alaiya, Chaker Adra, Fascin mediate breast cancer metastasis via regulation of metastasis-associated genes.
2. A poster was presented during the above mentioned meeting Monther Al-Alwan, Safiah Olabi1, Hazem Ghebeh, Eman

Barhoush, Asma Tulbah, Taher Tweigeri, Dahish Ajarim, Ayodele Alaiya, Chaker Adra , Fascin mediate breast cancer metastasis via regulation of metastasis-associated genes.

3. Fascin regulation of breast cancer cell morphology, migration and invasion has been established
4. Inhibition of fascin in breast cancer cells by chemotherapy, leading to reduction in migration and invasion was observed.
5. Fascin regulation of breast cancer chemotherapeutic resistance has been observed.
6. Identifying the molecular mechanism of fascin regulation of breast cancer migration and invasion is ongoing.
7. A manuscript has been submitted and another one is in preparation.

Project title

Clinical Proteomics: Development of Novel Biomarkers for Diagnosis of Ovarian Cancer, RAC # 2050 043, Funded By KACST

Principal Investigator: Dr. Ayodele Abdulkareem Alaiya

Co-Principal Investigator: Dr. Mai Al-Mohanna

Co-Investigators: Dr. Hany Al-Salem, Dr. Ismail Al- Badawi, Dr. Jamal Al-Subhi, Dr. Nada Al- Sahan, Dr. Asma Tulba MD and Dr. Osama Al-Omar

Project description

The goal of this work is to develop tools for the accurate classification of borderline tumors and differential diagnosis of pelvic tumor of unknown primary origin. We are using mini-2-DE gels technology which are rapid, simple and sensitive, thus making it especially applicable for routine tumor diagnosis.

Protein spots that differ significantly in their expression between benign and malignant tumors will be identified and used for objective and accurate molecular classification of borderline ovarian tumors and in particular in the differential diagnosis of borderline tumors and carcinomas.

Progress

1. The final report was submitted and accepted by KACST in March 2011
2. The identified differentially expressed proteins will be validated in archival materials
3. Manuscript in preparation.

Project title

Chronic Myeloid Leukemia: Development and Validation of Therapeutic Hematoproteomic Biomakers, RAC #2050 040

Principal Investigator: Dr. Ayodele Abdulkareem Alaiya

Co-Principal Investigators: Dr. Mahmoud Al-Jurf and Dr. Naeem Chaudhri

Co-Investigators: Dr. Mai Al-Mohanna , Dr. Entezam Sahovic, Dr. Fahad Al Mohareb, Dr. Fahad Al Sharif, Dr. Hamad Al Omar, Dr. Hazzaa Al Zahraniand Dr. Ali Al Shanqeeti

Project description

This project focuses on the analysis of global protein expression profiles in patients with Chronic Myeloid Leukemia in the chronic phase (CP CML). Peripheral blood (plasma/serum) and bone marrow samples from the same patients will be analyzed using 2-D gel electrophoresis and computer-assisted image analysis. Proteins of interest will be identified by peptide mass fingerprinting and sequencing. The goal is to identify novel protein biomarkers that will predict therapy response or disease resistance. This information will assist clinicians to develop customized treatment plans for patients individually.

Progress/Findings

1. Our preliminary data indicates that clinical and hematological responses at three months of Gleevec treatment can be predicted based on protein expression profiles of individual patients.
2. Sample collection is on going (43 samples have been collected so far). Chart review for extraction of clinical-pathological data for correlation of clinical features with protein expression patterns is on going for 3/6/12 month's treatment response.
3. Our results showed that bone marrow plasma proteome is more enriched than BM serum

Project title

Study of the Association between HLA-DRB1 Alleles and Vogt-koyanagi-Harada's Disease in Saudi Patients, RAC # 2050 034

Investigators: Khaled Al-Hussein and Khaled Tabara

Project description

Vogt-Koyanagi-Harada (VKH) disease is a potentially blinding disorder that afflicts the uvea in the eye leading to chronic inflammation. Associations with other auto-immune disorders have been reported. In Saudi Arabia, VKH has been found to be a common cause of uveitis as previously reported by Islam and Tabbara. Previous reports indicate certain HLA

genotypes show strong association with DRB1 *0405 and DRB1 *0410 and confer increased risk of VKH disease. It has been suggested that the HLA DRB1 gene is one of the candidate genes of VKH

Progress/Major Findings

1. Significant progress has been made and the project will soon be completed.
2. One paper has been published and another manuscript in preparation.
3. Our data indicates that Vogt-Koyanagi-Harada is associated with HLA-DRB1 *0405. Patients with VKH, in Saudi Arabia, may have genetic predisposition to environmental triggers that precipitate the clinical manifestations.

Project title

Clinical Cancer Proteomic: Understanding the Cellular and Molecular Biology of Prostate Tumors, RAC # 2050 026

Principal Investigator: Dr. Ayodele Abdulkareem Alaiya

Co-Principal Investigator: Dr. Ali Bin Mahfooz

Co-Investigators: Dr. Mai Al-Mohanna, Dr. Mohammad Aslam, Dr. Irfan Ahmed and Dr. Kamal Hanash

Project description

The gene expression of prostate tumors at the protein level will be studied by means of 2-D gel electrophoresis and computerized image analysis. The focus of this project is on the complex protein expression pattern of human prostate tumors, of varying malignancy potential, to identify proteins related to tumorigenesis, grade of aggressiveness, metastatic potential and treatment sensitivity. The aim is to find a correlation between altered tissue morphology and polypeptide expression. Ultimately this would complement the diagnostic markers already in the use, and commence a wider scan of the prostate proteome for carcinoma specific markers. Novel proteins will be characterized by highly sensitive mass spectrometry and if necessary sequence analysis.

Progress

1. A final report of the study was approved by ORA
2. Part of the finding has been published in International Journal of Oncology titled "Proteomics -based Signature for Human Benign Prostate Hyperplasia and Prostate Adenocarcinoma"; *Int. Jour. Oncol* 38: 1047-1057, (2011)

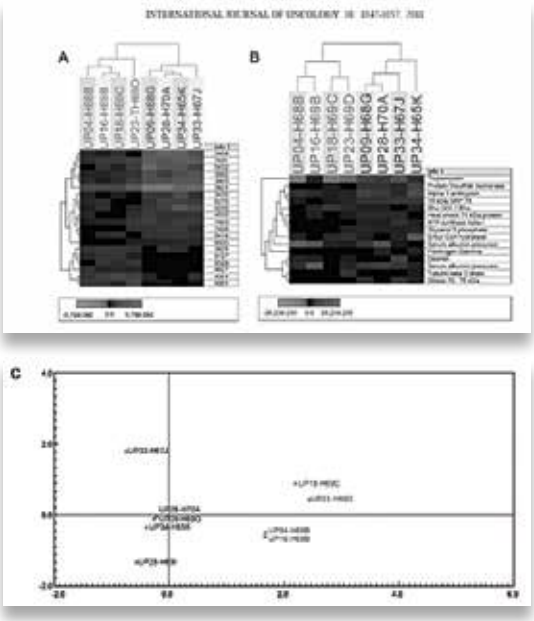

Figure 5. (A) Hierarchical Cluster analysis using the expression patterns of 20 proteins that are differentially expressed between Gleason 5 (low grade) and Gleason 7 (high grade) malignant prostate tumors. (B) Hierarchical Cluster analysis using the expression patterns of 15 proteins that have been identified both in this study and in previously published studies. The names of several of the identified proteins are indicated in the dendrogram (red, high grade Gleason 7; and blue, low-grade Gleason 5 cancers). The dendrogram was generated using the Bray Curtis distance metric and an average linkage clustering method from the J-Express software. (C) The correspondence analysis of the same dataset.

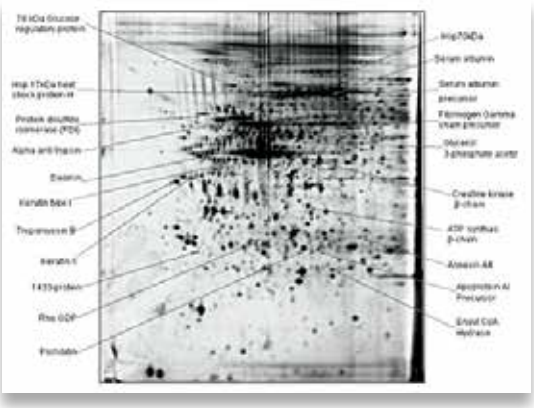

Figure 6. A representative 2-DE map derived from a prostate cancer sample. Marked are some of the identified proteins that differ between sample sub types. The proteins were identified by MALDI-TOF Mx Micro (Waters®, UK).

Project title

Protein Profiling: Understanding the Mechanisms of Tumor Responses to Therapy in a Mouse Model, RAC # 2050 014

Principal Investigator: Dr. Ayodele Abdulkareem Alaiya

Co-Investigators: Dr. Mai Al-Mohanna, Dr. Raafat El-Sayed and Dr. Falah Al-Mohanna

Project description

This pilot study is based on a mouse 4T1 breast tumor model. The 4T1 mammary carcinoma cell line is transplantable and tumors grow both in nude and BALB/c mice and in tissue culture. In addition the cells give rise to tumors that are invasive and that easily metastasize to distant sites, thus mimicking human mammary cancer. Complex protein mixtures from tissue and serum samples will be analyzed from the same individual animal using 2 D gel electrophoresis and computer assisted image analysis. Proteins of interest will be identified by peptide mass fingerprinting and sequencing. The aim is to identify groups of proteins involved in the mechanism of tumor response to therapy.

Progress

1. Protein identification by MALDI-TOF MS from tissue and serum samples is in progress
2. Final report has been submitted to ORA
3. Manuscript in preparation

Project title

Clinical Proteomics: Development of Novel Biomarkers for Translational Ovarian Cancer Research, RAC # 2050 011

Principal Investigator: Dr. Ayodele Abdulkareem Alaiya

Co-Principal Investigator: Dr. Mai Al-Mohanna

Co-Investigators: Dr. Ismail Al- Badawi, Dr. Hany Al-Salem, Dr. Jamal Al-Subhi, Dr. Nada Al- Sahan, Dr. Asma Tulba and Dr. Osama Omar

Project description

This project focuses on the analysis of global protein expression profiles in patients diagnosed with sporadic common epithelial ovarian tumor that are treated with conventional surgical and adjuvant therapy and/or cytoreductive and radiation therapy. The goal is to identify novel protein biomarkers capable of predicting patient's response to therapy and clinical outcome.

Progress

1. Project have been successfully completed and final report submitted and approved by ORA
2. Manuscript is in preparation.
3. Validation of identified proteins will be done in large archival material. This will be conducted as a new project to be submitted to ORA
4. Our findings showed that tumors of different malignant grades can be discriminated based on their protein expression patterns.
5. We are creating database for artificial disease classification of pelvic tumors based on differentially expressed proteins and efficient data mining as indicated in (figures 7 & 8).

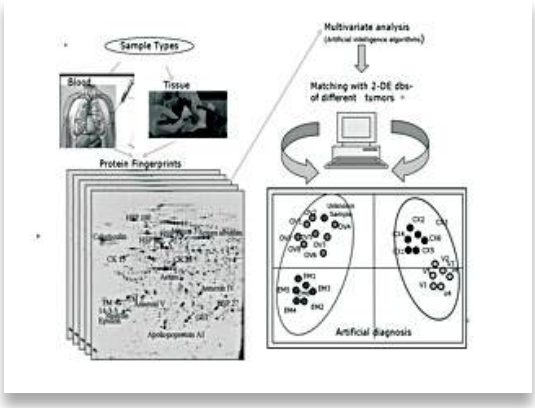

Figure 7. Schematic illustration of novel way of artificial tumor classification using multivariate data analysis of differentially expressed proteins. A- Tissue or blood sample is processed, B – Protein fingerprint is generated by 2-DE, C- Fingerprint images are deposited in tumor database for expression analysis, D –Computer assisted image analysis for artificial tumor classification.

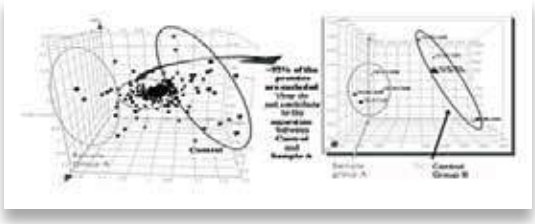

Figure 8. Data mining: Selection of significantly differentially expressed proteins that will be used for Molecular Classification of Tumors using Multivariate Analysis of Protein Expression Profiles.

Project title

Evaluation of Anti-Tumor Activity of γδ –T cells in Cancer Patients, RAC # 2030 022

Co-Investigators: Mahmoud Al-Jurf, Khaled Al-Hussein, Abdelghani Tbakhi, Hamad Al-Omar, Adher Al-Sayed and Ameera Gaafar

Project description

γδ T cells play an important role in innate and adaptive anti-tumor immunity. The task of innate effectors cells such as macrophages, NK cells, NKT cells, and γδT cells in tumor immuno- surveillance and tumor immunotherapy has recently been revisited. T cells bearing the TCRγδrepresent a minor subset of human peripheral T cells (1-10%), differing from αβT cells in cell surface phenotype. Their distribution and function in humans is less well characterized, though some evidence has been gathered indicating that γδT cells have been shown to exhibit major histocompatibility complex (MHC)-unrestricted cytotoxicity against some tumors. In addition, it has been recognized that donor-derived γδT-cell may serve as facilitating cells, promoting the engraftment of donor hematopoietic stem cells across varying degrees of MHC disparity. And yet, the in-depth position of γδT cells in the immune response of tumor patients remains largely elusive and controversial. In this study, we hypothesized that paucity in γδ T-cell frequency and immune function could be related to the development of breast cancer.

Progress Major Findings

Ex-vivo expansion of γδ T-cells by zoledronic acid may possibly amend this deficiency. Furthermore, the granzyme B gene was screened for a known single nucleotide polymorphism.

a. γδ -T cells were screened for the known granzyme B gene polymorphism in the breast cancer and normal controls. This study is completed and currently a manuscript is considered for publication by the journal of Experimental Hematology with major revision. An abstract is published in Exp.Hematol. and a final report is submitted and accepted by ORA.
b. Production and genetic mutation of perforin produced by γδ-T cells might contribute to the pathology and disease outcome of breast cancer patients. Currently we screened 66 normal and 10 breast cancer Saudi female donors. Data is being analyzed.

Project title

Proteomic analysis, anti-resorptive properties, and tumor cell cytotoxicity of osteodex in bone metastasis from breast and prostate cancer, Proposal # 2080 052

Principal Investigator: Dr. Ayodele A. Alaiya

Co- Principal Investigator: Dr. Chaker Adra

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

Project description

Our main goal in this study is to demonstrate that our compound, osteodex (ODX) have a direct anti-tumor effect as well as indirect effect through the inhibition of osteoclasts thereby decreasing the amount of tumor growth promoting molecules in primary tumor as well as in bone metastasis. In order to achieve some of our objective we have done some in vitro experiments and currently the in vivo animal model experiments are in progress.

Progress

1. Preliminary results showed that Osteodex induced ~85- 97% apoptosis at 10 μM in both breast MDA 231 and prostate PC3 cell lines, while the commercially available therapeutic agent Zometa failed to induce any significant apoptosis after 24 hrs treatments in any of the two cell lines at the tested concentration range (50 nM-10 μM) as shown in figure 9 below. Similar observation was observed at 48 hrs treatments (data not shown). Part of our findings on *in vitro* experiment resulted in one publication in Int Journal Oncology 2010

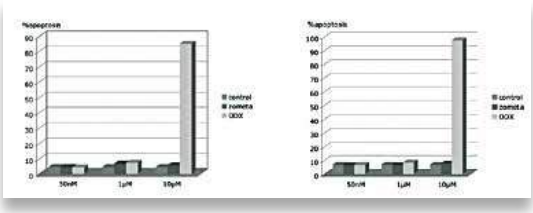

Figure 9. Effects of ODX and Zometa on treated PC3, MDA 231 and control cells: y axis = % apoptosis, x axis = concentration of test substance, mean values, n=2-3, cv = <10%.

Expression Proteomics

We treated cells with 10μM for global protein expression profiles between control and treated cells. The 10μM was chosen because it was the concentration that resulted in maximum effect of cell death in the apoptotic assay). Cells were treated with 10μM for different time periods ranging

from 3, 6, 18 & 24 hrs. Approximately 700 spots were resolved on 2-DE gels of which 62 spots were significantly differentially expressed and at least more than two-fold difference. (ANOVA, $p<0.05$).

The expression profiles demonstrated dose dependent changes among treated groups and clear separation from control untreated samples (Figure 10). A similar finding was observed in the PC3 prostate cancer cells (data not

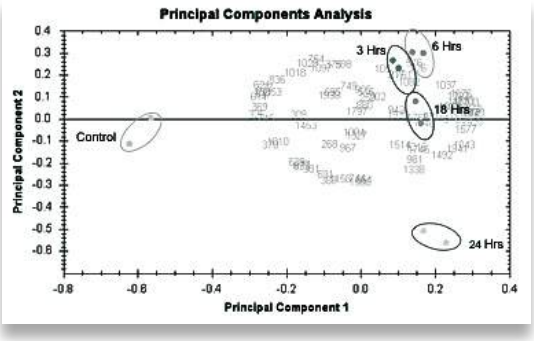

Figure 10. PCA analysis of differentially (< 2-fold change) expressed proteins between control cells and cell treated with different doses of ODX. (The observed different is significant by ANOVA, $P<0.05$).

shown).

2. *In vivo* experiment has commensed.

Summary

We have achieved part of the objectives of this study and have demonstrated the superior anti-tumor efficacy of our compound, osteodex (ODX) over one of the currently routine anti cancer agents. We plan to do caspase analysis to validate the mechanism of the tumor cell killing properties of ODX and to complete *in vivo* studies to evaluate its possible clinical usefulness in breast and prostate cancers with bone metastasis.

Project title

Identification of HLA Alleles in Normal Saudi Individuals by Sequence Based Typing, RAC # 2010-002 (AT-21 004)

Investigators: Khaled Al-Hussein and Abdelghani Tbakhi

Project description

The major histocompatibility complex (MHC) also referred to as Human Leukocytes Antigens (HLA) has been linked to the development of most autoimmune diseases, cancer, susceptibility to infectious agents and most importantly allograft rejection. Until recently, much of what is known regarding the population genetics of HLA in Saudi Arabia has been derived from the application of conventional methods and the alleles identified in Northern European and North American populations. The frequencies of HLA alleles however, vary considerably among different ethnic groups. The conventional techniques used by most laboratories, including those in Saudi Arabia, for HLA tissue typing are incapable of detecting all allelic variations with precision without information on their DNA sequences.

Progress

In this KACST approved project, 1000 healthy Saudi individuals, from various regions of the Kingdom of Saudi Arabia, was typed from their HLA allele using a valuable method known as Sequence Based Typing (SBT) whereby a spectrum of HLA Class I and II alleles was identified. This will facilitate the establishment of a Saudi HLA allele database. We have studied the frequency of HLA Class I (-A, -B, -C) alleles in 1000 normal Saudi individuals. Twenty-one HLA-A alleles were detected. HLA-A*0231 and HLA- A*3102/3104-5 were found to be the most frequent and the most diversified region in the HLA-Class I loci is the HLA-C Twenty-eight HLA-C alleles were detected.

Project title

HLA Gene association in Patients with Type 1 Diabetes in Saudi Arabia, RAC # 2000 029

Investigators: Khaled Al-Hussein and Mohammed Al-Ahmed

Project description, Progress and Major Findings

Type 1 diabetes is an autoimmune disease caused by a combination of genetic, immunological and environmental factors. It is mediated by both CD4+ and CD8+ T cells and result in the destruction of beta islet cells in the pancreas. Since T cells see the antigen in the context of the MHC-antigen complex, immunogenetic studies are imperative to decipher the interaction of both humoral and cellular mediated interaction in the auto-destruction of beta islet cells. . Previously (HLA) class II DQB1*0201/0202-DRB1*04 genotype was reported to be a predisposing allele to type 1 diabetes {insulin-dependent diabetes mellitus (IDDM)} in the Saudi Arabian population, whereas significant protection was found to be conferred by

DPB1*0401. Our reported data showed that high frequency of the DPB1*0104 allele, even in the presence of predisposing DQB1*2 allele, in healthy subjects may indicate a protective effect of this combination of HLA alleles against type 1 diabetes. In this project we used a larger cohort of control subjects and patients to confirm the above mentioned hypothesis that protective HLA class II genes can override the risk provided by HLA-DQ susceptibility alleles.

Project title

Study of the relationship between the genetic polymorphisms of the Natural Killer Cell receptor (KIR) genes and the outcome of the hematopoietic stem cell transplantation for hematological malignancies in Saudi Arabia, RAC # 2051001 (KACST: AT-26-03)

Investigators: Mahamoud Al-Jurf, Abdelghani Tbakhi, Ameera Gaafar Mohamed and Khaled Al-Hussein

Project description

Natural killer (NK) cells can mediate the acute rejection of bone marrow cell (BMC) allografts. The mechanisms underlying the rejection process remain unclear. NK cells express 1) inhibitory receptors specific for major histocompatibility complex (MHC) class I molecules and 2) activating receptors with diverse specificities. Inhibitory NK receptors confer to NK cells the ability to discriminate between MHC class I positive and negative target cells. Therefore they are involved in the control of NK cell tolerance to self and the elimination of cells that have down regulation of MHC class I molecules. Neither the KIR gene locus polymorphism nor the degree of KIR mismatch of our HLA donor-recipient transplant pairs has been identified in the Saudi population. Therefore, a prospective study that focuses on these two main aims is warranted .The purpose of this study is to investigate the effects of KIR incompatibilities in HLA- matched related donor-recipient pairs.

Progress

To date 60 healthy donor and 6 bone marrow transplant recipient samples have been screened. Whole blood was used to isolate genomic DNA. The method for typing the KIR genes was standardized. DNA typing was carried out using the Sequence Specific Primer (SSP) technique for the presence of different KIR loci. Similar to published data, we observed that the framework genes 2DL3, 2DL4 and 3DL3 were expressed in all (100 %) recipients, whereas 2DL4, 3DL2 and 3DL3 were expressed in all (100%)donors. While other genes varied in their frequencies, 2DS5, the activating KIR gene, was not expressed by recipients. Currently few samples have been typed. Thus it is difficult to present the exact scenario of the distribution of genes in the Saudi population. Collection of more blood samples from the clinic is needed to analyze the distribution pattern of KIR genes in the Saudi population and to understand the effect of HLA mismatching in relation to KIR. Based on preliminary results, further studies are currently underway.

Project title

Determination of the effect(s) of polymorphism (s) in specific genes controlling the immune responses in Saudi renal transplant patients, ,RAC # 2041081 (KACST: AT 25-41)

Investigators: Khalid Al-Meshari, Abdelgani Tbakhi, Ameera Gaafar and Khaled Al-Hussein

Project description

Transplantation is the ideal therapy for the majority of end-stage organ diseases. Organ transplantation, in Saudi Arabia, is a well-established modality in the treatment of organ failure. Genotyping profiles of the Natural killer cell Immunoglobulin-like receptors (KIR) have been reported to vary among different ethnic groups. This report represents a novel longitudinal study to investigate the underlying immune system genes, which contribute to graft survival or rejection in the Saudi population. New molecular markers will also be identified to predict the presence or absence of detrimental factors that underlay immune responses in clinical transplantation.

Progress

Genotyping profiles of the Natural killer cell Immunoglobulin-like receptors (KIR) have been reported to vary among different ethnic groups. We commenced a longitudinal study for the first time, to investigate the underlying immune system genes, which might contribute to the graft survival or rejection in Saudi population. We intended to identify new molecular markers in order to predict the presence or absence of detrimental factors underlying all immune responses in clinical transplantation. In addition, our main objective is to compare KIR distribution between kidney transplant donors and recipients.

Major Findings

Similar to most published data, we observed the dominance of the two framework genes 3DL2 and 3DL3which are present in all (100%) recipients and donors investigated so far. While the other KIR genes vary in their frequencies. We also observed

the predominance of AA1 genotype. Allograft rejection was observed in 14 (19%) recipients. No association was observed of KIR genotypes with rejected or stable graft. In addition, a polymerase chain reaction with sequence-specific primers was used to screen for the known cytokines SNPs within genes encoding IFN-γ, TGF-β, TNF-α, IL-6 and IL-10 in the same set of donors/ recipients' pairs mentioned above. We observed that low IL-10 productivity is positively correlated with stable graft. The project is progressing very well and almost 90% of its aims were fulfilled. Currently data is analyzed and a manuscript in preparation.

Project title

BCR/ABL Translocation Status and T-cell Stimulation Capacity of Dendritic cells Derived From CD34+ and CD34- Bone Marrow Compartments from Patients with Chronic Myeloid Leukemia, RAC#990 029

Principal Investigators: Dr. Khaled Al-Hussein and Dr. Hamad Al-Omar

Co-Investigators: Dr. Ameera Gaafar, Dr. M. Al Jurf, Dr. A. Iqbal, Dr. A. Tbakhi and Dr. Fahad Al-Mohareb

Progress

The project was re-activated on the 11th of January 2011. An abstract was published in Exp. Hematol. and a manuscript is being prepared.

Project title

A73 Gene in Nasppharyngeal Carcinoma and its Oncogenic Potential, RAC# 2090 004

Principal Investigator: Dr. Maha Al-Mozaini

Co-Investigators: Dr. Mohammed Al-Ahdal and Dr. Asma Tulba

Progress

1. Submitted to ORA/KACST 30 December 2008. Almost half of the project is completed.

Project title

Detection and Mutations within the UL97 Geme of Ganciclovir – Resistant Cytomegalovirus in Clinical Isolates, RAC#2090 003

Principal Investigator: Dr. Maha Al-Mozaini

Co-Investigators: Dr. Mohammed Al-Ahdal, Dr. Sahar Al-Thawadi and Dr. Sami Al-Hajar

Progress

1. Submitted to ORA/KACST, 2008 Dec. No. data yet.

Project title

The Efficacy of Immunophenotyping and Molecular Studies in Improving Diagnosis, Sub typing and Management of Hematological Malignancies in Saudi, RAC # 2080 053

Principal Investigators: Dr. Saleh Al-Othman and Dr. Chaker Adra

Co-Investigators: Dr. Hussa Al-Hussaini, Dr. Mohammed Al-Dahmesh and Dr. Nasser Al-Thubiti

Progress

1. REC Accepted and recommended the proposal for Approval.
2. The proposal was forwarded to KACST as an Annual Grants Program.Unfortunately, it was not funded. Proposal was resubmitted for review by the scientific committee.

2011 SUBMITTED PROJECTS:

Project title

Functional Properties of Dendritic cells in Saudi HIV-1 Elite Controllers, RAC# 2110-001

Principal Investigator: Dr. Maha Al-Mozaini

Co- Investigator: Dr. Abdullah Al-Hokail, Dr. Mathias Lichterfeld, Dr. Chaker Adra and Dr. Xu Yu

Project title

Modeling of Immunosuppression and Clinical Trials in Renal Transplant, RAC# 2111-005

Principal Investigator: Dr. Maha Al-Mozaini

Co- Investigator: Prof. Eric Rosenberg, Dr. Khalid Al-Meshari, Dr. Mathias Lichterfeld, Dr. Chaker Adra, Prof. Maria Davidian (Project Consultant) and Prof. H.T. Banks (Project Consultant)

Project title

Molecular and Immunological Characterization of Dendritic Cells Generated from Primitive CD34 - Haematopoetic Stem Cells in AML & CML Patients: Clinical Applications in Adoptive Immunotherapy, RAC# 2110 007 (A-L 11-0425)

Principal Investigator: Dr. Khaled Al-Hussein

Co-Investigator: Dr. Chaker Adra, Dr. Fahad Al-Mohareband Dr. Ameera Gaafar

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Stem Cell Therapy Program / RC Staff

Director / Principal Scientist	Dr. Chaker N. Adra
Administrative Assistant	Madeline Fiji Schuck - Ranera Maria Linda Rasing -Macasieb
Senior Scientist	Dr. Khaled Al-Hussein
Scientists	Dr. Ayodele Alaiya Dr. Monther Al-Alwan
Associate Scientists	Dr. Hazem Ghebeh
Adjunct/Joint Scientists	Dr. Bandar Al-Saud Dr. Fadia El-Bitar Dr. Faten Al-Zamel Dr. Ismail Al-Badawi Dr. Zikra Al-Khayal Dr. Mamdouh Al-Baqumi
Post Doctoral Fellows	Dr. Ameera Gaafar Mohamad Dr. Andrew Wetzig Dr. Ibrahim Al-Duraibi
Assistant Scientist	Dr. Fadi Masharqa
Research Associates	Manogaran Pulicat Amer Al-Mazrou
Research Assistants	Abdullah Ben Sulaiman - Scholarship Program Ghida Sleiman Abdullah Al-Dhfyan
Research Technicians	Eyad Al-Humaidan Eman Yousef – KACST/NCPST Grant Safiah Olabi – KACST/NCPST Grant Zakia Shinwari – RC Grant Alia Iqniebi – RC Grant Abeer Al-Omair – Schorlarship Program Jamal Al-Ruwaili – Scholarship Program
Research Technical Assistants:	Christian Benedict Pradez – KACST/NCPST Grant Aseel Al-Otieschan – RC-Grant

Postdoctoral Trainee

- Dr. Khaldoun Al-Romaih – Scholarship Program
- Dr. Maha Al-Mozaini – Scholarship Program

Graduate Students

- **Kholoud Al-Saud:** Obtained M.Sc. (with distinction). The thesis was titled: "Immunological studies of primary cultured breast cancer cell lines isolated from Saudi Patient". The degree was awarded with arrangement with King Saud University, College of Applied Medical Sciences.
- **Ghofran Al-Qudaihi:** Obtained Ph.D. The thesis was titled: Investigation of M-Phase Phosphoprotein (MPP11) as a novel target for Leukemia T Cell Immunotherapy.

The degree was awarded with arrangment with University of Newcastle Upontyne, Newcastle Upontyne, United Kigndom.

- **Layla Al-Mansouri:** Started her Ph.D. program in Stem Cell Therapy Program, Research Centre, and now she is presuming the degree in University of Toronto, Canada.

Alfaisal University Summer Trainees

- Ahmad Hazem Adi
- Malik Mohammad Kanaan Nassan
- Mohammad Abdulrahman Aboummoh
- Mohammad Iffat Kabir Anindo
- Mohammad Fahmi Mathbout

Hosted Students/Trainees from different universities

International	
Name	Degree/Universities
Asmaa Al-Harbi	Ph.D. Student, Newcastle University,UK
Bashir Elkum	Medical Student Weill Cornell, Qatar
Christian Benedict Pradez	BSc Trainee, Arellano University, Philippines
Hanan Aman	BSc Trainee, Qatar University, Qatar
Hayat Aman	BSc Trainee, Qatar University, Qatar
Layla Al-Mansouri	PhD Student, University College London, UK
Sameena Anwar	MSc Trainee, University of London, UK
Sherin Abdul Basheer	BSe, Vinayaka Missions University, India
National	
Name	Degree/Universities
Abdullah AlMshari	BSc Student, King Saud University
Abeer Al Agily	BSc Trainee, King Saud University
Abeer Al-Mimah	MSc Trainee, Umm Al-Qura University
Ahmad Adi	Medical Student, Alfaisal University
Albara Marwa	Medical Student, King Saud University
Ali Al-Sagheir	BSc Trainee, King Saud University
Amal Al Thubaity	BSc Trainee, King Abdulaziz City
Amal Jaafar	BSc Trainee, King Saud University
Dalal Baljoon	BSc Trainee, King Saud University
Dunia Jawdat	BSc Trainee, King Saud University
Gelowi Asiri	BSc Trainee, King Saud University
Ghofran Al-Qudaihi	PhD Student, King Khalid Foundation
Hadeel Al-Houri	BSc Trainee, King Saud University
Hanady Al-Rasheed	BSc Trainee, King Saud University
Ibrahim Marwa	Medical Student, King Saud University
Ibreez Al-Khuraiyf	BSc Trainee, King Saud University
Kholoud Al-Saud	MSc Student, King Saud University
Kholoud Al-Homoudi	BSc Trainee, King Saud University
Lamia Fahad	BSc Trainee, King Saud University
Malik Nassan	Medical Student, Alfaisal University

National (cont.)	
Name	Name
Mansour Alghamdi	The University of Western Australia
Mashal Al-Wadani	Medical Student, King Saud University
Mohammad Abouammoh	Medical Student, King Saud University
Mohammad Anindo	Medical Student, Alfaisal University
Mohammad Mathbout	Medical Student, Alfaisal University
Nashwa Othman	MSc Trainee, King Saud University
Najla Al-Yamani	Medical Student, King Saud University
Nihal Al-Muraiki	BSc Trainee, King Faisal University
Nouf Al-Oily	BSc Trainee, King Faisal University
Reem Alsulaimani	MSc Trainee, King Saud University
Rola Qarrash	BSc Trainee, King Saud University
Saeed Al-Qarni	BSc Trainee, King Saud University
Safa Al-Yamani	BSc Trainee, King Saud University
Samiyah Alkhaldi	BSc Trainee, Umm Al-Qura University
Sawsan Bagabas	BSc Trainee, King Saud University
Sawsan Barhoush	BSc Trainee, King Saud University
Shaheerah Asiri	BSc Trainee, King Saud University
Turki Al-Sudairy	BSc Trainee, Al Farabi Colleges
Wadha Bukhari	BSc Trainee, Al Farabi Colleges
BSc Trainee, King Saud University	BSc Trainee, King Saud University
Yasser Basmaiel	BSc Trainee, King Saud University

The

Research Centre
Training & Education Office

The Research Centre Training & Education Office

Director

Khawla S. Al-Kuraya, MD FCAP

Staff

Committee Members

Ahmed Al-Qahtani, PhD
Abdelilah Aboussekhra, PhD
MohammedElfaki, PhD
Nada AlTassan, PhD
Omer Demirkaya, PhD
Faisal Al-Rumayan, PhD
Abdullah Assiri, DVM, PhD
Bushra Siddiqui, MSc
Edward Hitti, PhD
Saleh Al-Othman, PhD
Abdul Khalid Siraj, PhD
Huda Al-Mosallam
Faten Al-Khateeb

Administrative Staff

Huda Al-Mosallam - Manager
Faten Al-Khateeb – Course Coordinator
Abdulrahman Al-Lahoo - Coordinator
Gina Rodil - Secretary
Lama Sultan - Secretary
Arwa Fayyad – Bilingual Secretary
Sara Abu Raad – Bilingual Secretary

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 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. RC-TEO organizes and conducts Special Courses, Workshops, Symposia and other events throughout the year.

EXPERTISE

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

ACTIVITIES

The Research 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	Total	Completed
Postdoc Fellow	4	1

Hospital Scholarship Program

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

Recipient	Total	Completed (Cancelled)
PhD	12	1
MSc	6	2 (2)
BSc	1	0

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.

Recipient	Total	Completed
PhD	7	7
MSc	15	4

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
- Medical Fellows/Residents for training in Research Methodology
- High School students interested in a career in Biomedical Sciences can be given a short orientation

Program	Completed
I-H TP	107

Future Scientists Program (FSP)

The aim of this program are to assist talented young male high school Saudi nationals in the acquisition of scientific skills, to help them appreciate science and its value to humanity, and to prepare them for a future in the field of Biomedical Sciences by providing an environment for their scientific growth.

Program	Completed
FSP	12

Ibn Sena Program (ISP)

An agreement was created in 2006 between KFSH&RC-Research Centre and King Abdulaziz and his Companions Foundations for Giftedness & Creativity to assist talented young Saudi nationals to integrate their scientific skills/talents in preparing them in different areas of Science in the future.

Program	Completed
ISP	26

Al Razi Summer Training Program (ARSTP)

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

Program	Completed
ARSTP	28

Al Faisal Program (AFP)

A collaboration between KFSH&RC and AlFaisal University is established to give the medical students an orientation in the laboratory and allow them to present their assigned topic and experiment.

Program	Completed
AFP	2

Research Center Seminars (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	Total	Attendees
RCS	37	1146

Workshops, Courses and Conferences (WS&Conf)

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

Program	Total	Attendees
WS, C&Conf	6	680

THE

MEDICAL AND CLINICAL AFFAIRS

RESEARCH REPORT

THE DEPARTMENT OF

Dentistry

The Department of Dentistry

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 # 991030

Investigators: Dr Aziza Al-Johar, Dr Kandasamy Ravichandran, Ms Shazia Subhani

Project description

Objective: To report the patterns of craniofacial anomalies in Saudi Arabia

Design and Setting: Data from a hospital registry, based at a tertiary care center.

Patients: Craniofacial patients registered during 2002-2008 in the Cleft lip/palate and craniofacial anomalies registry at King Faisal Specialist Hospital & Research Centre, Riyadh.

Results: Out of the 411 craniofacial cases (M=223; F=188), 168 cases had cranial anomalies, 311 cases had facial anomalies with 68 cases overlapping both the conditions. Craniosynostosis, accounting to 33.1% of total cases, was seen in 75 male and 61 female. Out of the 66 cranial syndromic cases, Apert syndrome and Crouzon syndrome was seen in 25 and 18 cases, respectively. Among facial anomalies, Dysmorphic features were often observed (35) followed by protruded premaxilla (20) and micrognathia(18). Among facial syndrome, Pierre Robin sequence (66), Goldenfar syndrome (18) and Van der Woude syndrome(16) was observed. Among associated deformities of CL/P, cleft palate (160; 57.8%) was more common, followed by cleft lip and palate (87; 31.4%) and cleft lip (23; 8.3%). Out of the 208 cases having other congenital anomalies, cardiovascular is the most commonly affected system with 34 children. Significantly (p=0.01) more family history of anomalies was observed in children born to parents whose marriages among first cousin than in children born to parents whose marriages were not among first cousin.

Conclusion: The pattern of craniofacial anomalies observed in this study does not differ significantly from those reported in the literature.

Publication

Submitted for publication in the Saudi Medical Journal, November 2010.

Project title

Registry of Cleft Lip/Palate and Craniofacial Anomalies"

RAC #: 991030Investigators: 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 occurrences of craniofacial anomalies and is the foundation for the epidemiological research needed to evaluate the clusters.

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

Progress

On-going project.

Project title

Modeling Familial Aggregation of Cleft Lip/Palate: A Hospital Based Registry, RAC # 2101004

Investigators: Dr. Ravichandrean Kandasamy, Dr. Mohamed Shoukri, Dr. Yasmin Al Twaijri, Dr Aziza Al-Johar and Ms. Shazia Subhani

Project description

Abstract: Several studies showed Cleft lip/palate (CL/P) are known to recur in families with the risk of having a second infant with CL/P after given birth to a first infant with same defect varies among women. A high risk of having infants with birth defects can result from maternal or paternal genes, dietary

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

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

Objectives:

(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

(iii) To assess the possible effect of consanguinity and gender on the risk of cleft lip/palate.

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

PUBLICATION

Submitted for publication in the American Journal of Medical Genetics, March 2011

Project title

Measurement of Treatment Outcome in the Cleft Lip and Palate Patients in King Faisal Specialist Hospital & Research Centre, Saudi Arabia, RAC # 2091017

Investigator: Dr Aziza Al Johar

Project description

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

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

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

Specific Aims & Objectives:

1. To evaluate the clinical outcome of cleft care at KFSHRC
2. To identify risk factors for poor outcome
3. To address the health needs of these patients
4. To have periodic evaluation of cleft records and protocol

Objectives of the study:

1. To examine existing records using different clinical tool
2. To collect records of different clinical outcomes for cleft children
3. 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.

Progress

On-going project.

Project title

Genetics of Craniofacial Birth Defects in Saudi Arabia, RAC 2080006

Investigators: Dr Fouzan Al Kuraya and Dr. Aziza Al Johar

Project description

Abstract: Birth defects are important cause of disability worldwide with tremendous impact on the public health system. Craniofacial birth defects are particularly important because, as a group, they represent the second most common class of birth defects in humans. Additionally, they affect a region in the body that's readily observable by others thereby compounding the psychological component of the disability. The cause of most birth defects is unknown. Genetic, nutritional, infectious, and

other environmental factors, contribute to the total incidence of birth defects, but the percentage attribute to each is not known. In Saudi Arabia several factors make it likely that genetic etiologies contribute more significantly to craniofacial birth defects than other parts of the world. Perhaps the most important of these factors is the high frequency of autosomal recessive disorders (many of which will inevitably involve the complex structure of the face and other craniofacial structures) as a result of high degree of inbreeding and consanguinity. One research group has an extensive experience in mapping mendelian disorders, including genetic conditions associated with craniofacial anomalies. Similarly, we have solid expertise in the areas of clinical, molecular and developmental genetics. We propose to focus our existing expertise direction of dissecting the molecular defects that underline craniofacial birth defects in Saudi Arabia. Characterizing these mutations will have an obvious impact on the medical care of the affected individuals since it makes prenatal/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:

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

Progress

On-going project

Project title

The Incidence of Oral Mucositis in Pediatric Hematopoietic Cell Transplantation, RAC # 2091015

Investigators: Dr Zikra AlKhayal, Dr Mouhab Ayas, Dr. Mohammed Al Helal, Dr. Abdullah Al Jefri, Dr. Amal Al Seraihi and 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:

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

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

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

Progress

On-going

Project title

The Propagation of Mesenchymal and Neural Stem Cells from Adult Olfactory Mucosa, RAC 2080007

Investigators: Dr. Chaker Adra (PI) and Dr. Zikra AlKhayal

Project description

Abstract: Recent investigations into the treatment of spinal cord injuries using stem cell therapy have shown promising results. The majority of studies utilize non-neural tissue as a source of stem cells. In particular, mesenchymal stem cells have been utilized in transplantation experiments to treat animal modes of neural disorders. Upon transplantation mesenchymal stem cells allow functional improvement by providing immunosuppressive and neurotrophic support. However, mesenchymal stem cells, largely, fail to differentiate when transplanted. The human olfactory epithelium is an accessible source stem cells. The lamina propria of the olfactory mucosa contains mesenchymal tissue that may house mesenchymal stem sells. The epithelium of the olfactory mucosa may contain a neural stem cell population. As an inherently neural stem cell population, olfactory neural stem cells may be more likely to differentiate into appropriate neural phenotypes upon transplantation than non-neural stem cells. Therefore the human olfactory mucosa may be a source of both neural stem cells and mesenchymal stem cells for therapeutic use.

Hypothesis: Both neural and mesenchymal stem cells can be derived from the human adult olfactory mucosa using animal serum free techniques

Aims:

1. To determine the presence of mesenchymal stem cells in the olfactory mucosa.
2. To develop animal serum free techniques for the culture of mesenchymal stem cells with mesenchymal and neural stem cells from the adult olfactory mucosa
3. To compare olfactory mesenchymal stem cells with mesenchymal stem cells derived from the bone marrow and umbilical cord examining their specific protein 'fingerprint'.

Methods: The study will use cell isolation and isolation of mesenchymal stem cells from olfactory muscosa

Progress

On-going

THE SECTION OF PROSTHODONTICS

Project title

Rare Dental Disorder Registry, RAC # 2071082

Investigators: Dr Adeeb Al Omrani (PI), Dr Hans Hansson, Dr Richard Hakansson, Dr Khalid Al Zoman, Ms Shazia Naz Subhani

Project description

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

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

Progress

On-going.

Project title

Gene Expression & Immuno-Histological Findings in Patients with Papillon Lefèvre Syndrome, RAC # 2070022

Investigators: Adeeb Al Omrani BDS, DMSc (PI), Namik Kaya, PhD (Co-PI), Saleh Al-Muhsen, MD, Dilek Colak, PhD, Hamad Al Zaidan, MD, Said Dermime, PhD, Mohammed Al Owain, MD, Hazem Ghebeh, PhD, Richard Hakansson, DDS, PhD and Christer Ullbro, DDS, PhD

Project description

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

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

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

1. Comprehensive genetic assessment:
   - Gene expression profiling of PLS patients, carriers and controls in the blood and patients, and controls in gingival tissue.
2. Study the immunologic status of PLS from blood samples:
   - Detailed neutrophils function including: adhesion (by means of CD11/CD18 expression) chemo taxis, phagocytosis and killing abilities (by evaluating the oxidative burst function).
   - Lymphocytes phenotypic distribution, and lymphocytes proliferation assays.
   - Natural Killer cytotoxic activity.

Progress

On-going.

THE SECTION OF PERIODONTICS

Project title

Prevalence of Undiagnosed Type 2 Diabetes, Impaired Fasting Glucose, and Impaired Glucose Tolerance in Patients Visiting Dental Clinics RAC # 2101009

Investigators: Dr. Khalid Al Zoman, Dr. Sultan Mubarak, Dr. Hussein Naif, Dr. Ali Al Ghamdi

Purpose

The purpose of the study is to investigate the prevalence of undiagnosed type 2 diabetes, impaired fasting glucose, and impaired glucose tolerance in patients visiting dental clinics at King Abdulaziz University, King Faisal Specialist Hospital & RC in Riyadh, and King Fahad Medical City, Riyadh.

Objectives

1. To have knowledge about the prevalence of undiagnosed type 2 diabetes, impaired fasting glucose, and impaired glucose tolerance in patients visiting dental clinics.
2. To find if medical history, dental history, family history and signs and symptoms of diabetes will help to diagnose undiagnosed cases of diabetes mellitus (type 2) and pre-diabetic conditions.
3. To suggests guidelines that may help to diagnose undiagnosed cases of diabetes and pre-diabetes by dental health providers.
4. To evaluate the need for combined medical–dental examination for diabetic patients as new standard to improve preventive and treatment procedures.
5. To have a baseline study for longitudinal studies on diagnosis of pre-diabetic conditions and undiagnosed diabetes by dental health care providers.

Research Design & Methodology

Study Design: Multi-center, Cross-sectional study

Study Protocol: Data will be randomly collected from patients (age 40 years and older) visiting the dental clinics at King Abdulaziz University, King Faisal Specialist Hospital & RC in Riyadh, and King Fahad Medical City, Riyadh. One thousand and fifty patients are needed to complete the study. Known diabetic patients, patients <40 years and pregnant women will be excluded from the study. Data including patient age, sex, nationality, marital status, habits, and allergies will be recorded. An extensive medical history, family history, and dental history will be taken from each patient. The presence of any signs and/or symptoms of diabetes will be investigated. Patient's weight and body mass index (BMI) will be recorded.

Progress

On-going.

THE DEPARTMENT OF

Emergency Medicine

Department of Emergency Medicine

Research Coordinator
Hameed Ullah Khan, MD

The department undertook many research projects during year 2010. However only one project was completed. This project is in a process of publication. Three chapters were published in different books. The detail is given below

DETAILS OF THE RESEARCH ACTIVITIES

Project title

Canadian Emergency Department Triage and Aquity Scale: Implementation in a tertiary care centre in Saudi Arabia.

Investigator: Naser Elkum, CarolAnne Barrett, Hisham Al-Omran.

Project description

Objective: To describe the results of Emergency department waiting time after the implementation of the Canadian Triage and Aquity scale (CTAS) in a major tertiary care hospital emergency department outside of Canada.

Design: Retrospective study

Setting: King Faisal Specialist Hospital and Research Centre (KFSHRC).

Study population/sample: A total 1206 charts of those presented to ER at KFSHRC

Main results: The approximate time to triage was ≤ 10 minutes for 71% and ≤ 15 minutes for 82% of the patients. Fifty-three percent (53.5%) completed their triage process within 5 minutes. Waiting times be evaluated by a physician was 100% within CTAS time objectives in category I patients, however this was not the case for the other 4 categories. The overall left without being seen (LWBS) rate was 9.8%; 11.9% were in Level III, 20.3% in Level IV and 67.8% in Level V. Median length of stay (LOS) was 144 minutes for the study sample as a whole.

Conclusion: The CTAS may be adapted, with achievable objectives, in hospital outside Canada as well. Time to see physician, total LOS, and LWBS are effective markers of performance of ED and the quality of triage. RTP and LOS profiles, stratified by triage level, are essential for the management of ED and improving patient flow through collaborative efforts.

Details of publication of chapters in books

1. Hypoglycemia and Metabolic Emergencies in Infants and children. Nadeemuddin Qureshi, Muhammed Al-Mogbil, Osama Y. Kentab. Chapter 137. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th Edition.
2. Neck Masses in Children. Osama Y. Kentab, Nadeemuddin Qureshi. Chapter 118. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th Edition.
3. Pediatric procedures. Nadeemudin Qureshi, Mohammed Al Mogbil, Khalid Abu Haimed. Pediatric Procedures, Chapter 41, PP 505-537. Global EMS 2010.

THE DEPARTMENT OF

Family Medicine and Polyclinics

Department of Family Medicine and Polyclinics

Chairman
Abdullah Alkhenizan, MD

The Department of Family Medicine and Polyclinics has revitalized its efforts to balance staff productivity in terms of clinical and academic aspects. With the provision of greater incentives to do research studies, a good number of proposals were submitted. The restructured Departmental research committee has formulated an aggressive plan to be able to pool staff resources and clinical data available in the Department. Collaboration with ITA-ICIS, Medical Records, Quality Management Department are in progress in order to translate the clinical data into research studies that will enhance the physicians' standards of patient care in King Faisal Specialist Hospital and Research Centre (Gen. Org.).

RESEARCH ACTIVITIES

Project title

The Role 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: 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 Alkhenizan, MD, Abdulaziz Al Nasser, MD, Abdulaziz Al Saif, MD, Kevin Hafez, 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 Standards

Principal investigator: Abdullah Al Khenizan, MD

Co-investigator: Prof. Charles Shaw

Project title

Prevalence of HPV Genital Infection in Saudi Women. A Multi Center Study

Principal investigator: Ishmail Badawi, MD

Co-investigator: Tarfah Muammar, MD

PUBLICATIONS

- Efficacy of steroids or acupuncture for Bell's palsy. Amer Sheikh, Abdullah Alkhenizan, *Acupunct Med*. 2010 Mar;28(1):56
- Assessment of the accreditation standards of the Central Board for Accreditation of Healthcare Institutions in Saudi Arabia against the principles of the International Society for Quality in Health Care (ISQua). Abdullah Alkhenizan, *Annals of Saudi Medicine*.
- Updated Recommendations for the Diagnosis and Management of Osteoporosis: A Local Perspective [pg.111] Hussein Raef, Munira Al-Bugami, Sakra Balharith, Mahmoud Moawad, Mohammad El-Shaker, Aneela Hussain, Ahmad Al-Shaikh, Ismail Al-Badawi
- Ovarian Cancer. Green AE, Ahmed S, Al Husaini HH, Hussain AN,et al. eMedicine from WebMD. Updated March 29, 2011. Available at: *http://emedicine.medscape.com/article/255771-overview*.
- Gynecologic Tumor Markers. Hussain F, Hussain AN. eMedicine from WebMD. Updated March 29, 2011. Available at: http://emedicine.medscape.com/article/269839-overview.
- Type 1 Diabetes Mellitus. Khardori R, Bessen HA, Hussain AN, et al. eMedicine from WebMD. Updated March 29, 2011. Available at: *http://emedicine.medscape.com/article/117739-overview*.
- The roles of apo E genotype, gender and adipokines in blood plasma lipids in Caucasians with well-controlled type 2 diabetes. *International Journal of Diabetes and Metabolism*. 18:49-52. Co-Author: Kevin Hafez
- Gender differential in apo E genotypes' correlative tendency to dyslipidaemia responsiveness upon flaxseed oil administration in adult type 2 diabetic patients not meeting the 2008 Canadian Practice Guidelines. *International Journal of Diabetes and Metabolism*. 18:99-113. Co-Author: Kevin Hafez
- Allogeneic stem cell transplantation using myeloablative and reduced-intensity conditioning in patients with major histocompatibility complex class II deficiency. Al-Mousa H, Al-Shammari Z, Al-Ghonaium A, Al-Dhekri H, Al-Muhsen S, Al-Saud B, Arnaout R, Al-Seraihy A, Al-Jefri A, Al-Ahmari A, Ayas M, El-Solh H. *Biol Blood Marrow Transplant*. 2010 Jun;16(6):818-23.
- 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.
- Swyer-James MacLeod Syndrome in a 60-Year Old Patient. Patricia McWalter, Amal Alshmmasi, (submitted for publication to *Annals of Thoracic Medicine*).

THE DEPARTMENT OF

Liver Transplant & Hepatobiliary & Pancreatic Surgery

Department of Liver Transplant & Hepatobiliary & Pancreatic Surgery

Chairman
Mohammed Al Sebayel, MD

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). There were three research proposals that have been submitted to RAC for approval in 2010. These proposals are still on process in completing necessary requirements requested by the REC. Journal Articles were published in the year 2010 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.

APPROVED RESEARCH ACTIVITIES

Project title

Pan Arab Liver Transplantation Registry, RAC No: 2071 022
Investigators: Hatem Khalaf, MD, Mohammed Al Sebayel, MD

Project description

Establishing a web-based Liver Transplantation registry aiming to monitor Liver Transplantation activities in KFSH& RC and towards the Arab World hoping for better follow-up and care for liver transplant patients. The project objectives include the following:

1. To obtain the frequency of liver transplantation activity in 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 2010:

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 and King Fahad Specialist Hospital in Dammam are on process to incorporate their transplant data in this registry. Orientation and training has already been scheduled.

Phase III (Liver Transplant patients in Arab World): Cairo University updates liver transplant patients' data in the registry in a timely manner.

Project title

Microsurgery Training, RAC No: 2082003
Investigator: Mohammed Al Sebayel, MD

Progress & Major Findings

This training has been put on hold until further notice due to severe shortage of staff and remarkable increase in the number of liver transplant surgery in 2010:

THE DEPARTMENT OF

Medicine

The Department of Medicine

Chairman
Hamad Al-Ashgar, MD

There were 2 projects in the field of Hepatology concerning chronic hepatitis B and C was completed in the section of Gastroenterology in the year 2010.

The 1st project entitiled "Efficacy of Peginterferon α-2a and Predictors of Response in HBeAg-negative, Genotype D Naïve Patients" (RAC No 2051045) was a prospective multicenter clinical trial, which involved 4 tertiary referral Hospital in Riyadh, included KFSH&RC, King Abdulaziz Medical City (KAMC), Armed Force Hospital (AFH) and King Saud University Liver Disease Research Center. The study was started in 2006 and finished in 2010. The full paper has already been written and in process for publication (in Hepatology International). Treatment of chronic hepatitis B with currently available oral nucleoside/ nucleotide analogues may be associated with development of drug resistance and relapse after discontinuation of therapy. Thus, more efficacious therapies are needed that can suppress HBV for a longer duration after discontinuation of antiviral therapy without the development drug-induced viral mutation. Peginterferon (PEG-IFN) α-2a has both antiviral and immunomodulatory effects that may be associated with long-term viral suppression This is the first prospective multicenter study in the literature that describes the efficacy of PEG-IFN α-2a in HBeAg-negative CHB genotype D naive patients from the Middle East and provided a detail analysis of baseline and on treatment predictors of response. The present study of CHB genotype D patients showed a higher response (SVR of 57.1%) than previously reported, as based on the earlier, definition of SVR (HBV DNA <20,000 copies/mL). The study has already completed but the follow up of the patients is still continuing to observe the long term sustained viral remission in patients who developed sustained viral response.

The 2nd project (RAC: No. 2081 101) was a retrospective study of 64 consecutive adult chronic HCV patients, who were treated with combination therapy of α-2a PEG INF and Ribavirin for 48 weeks from 2006-2009 in KFSH&RC, their stored pre-treatment serum samples collected for routine HCV quantification and genotyping in the molecular diagnostics laboratory were retrieved, and assessed for HCV-4 sub genotypes and IP-10 levels. HCV-4 heterogeneity is not known in Saudi Arabia and its knowledge is crucial for clinical and epidemiological analyses that will be required for the development of effective vaccines and antiviral therapies against HCV-4. The role of IP-10 level in predicting response to combination therapy in various sub-genotypes of HCV-4 was never reported in literature as best of our knowledge and worth studying. We recognized that genotype 4a and 4d are the commonest genotypes in Saudi Arabia, where genotype 4a conceded a better chance of SVR than 4d. There was a significant association between the low baseline IP-10 level and good response to treatment in HCV genotype 4 patients. When we analyzed genotype 4a and 4d separately, then 4d level is significantly low in patients who achieved SVR suggested that low level of IP-10 in genotype 4d is a predictor of response. Our findings concluded the incidence and treatment response of various sub-genotypes of HCV genotype 4 in Saudi Arabia and showed their correlation with the IP-10 levels as a predictor of response but these findings should be analyzed further in a larger prospective multicenter trials.

Project title

Efficacy of Peginterferon α-2a and Predictors of Response in HBeAg-negative, Genotype D Naïve Patients

Investigators: Hamad I Al-Ashgar, Mohammed Q Khan, Abdulrahman Aljumah, Faisal M Sanai, Ayman A Abdo, Mutasim M Dafalla, Mosa A Fagih, Khalid I Bzeizi†.

Project description

Background: Peginterferon (PEG-INF) α-2a has been shown to induce a sustained virological response (SVR) in 20-30% of HBeAg-negative patients. Aim: To determine the safety and efficacy of PEG-INF α-2a in HBeAg-negative, genotype D naïve patients and to analyze the predictors of response.

Methods: This prospective, multicenter, open-label, nonrandomized trial was conducted at four hospitals. Thirty five consecutive HBeAg-negative naive genotype D patients received PEG IFN α-2a for 48 weeks.

Results: Based on a cutoff of HBV DNA <400 copies/mL, an early virological response (EVR) at week 12, end of treatment virological response (ETVR) at week 48 and SVR at week 72 were achieved by 3 patients (9%), 9 patients (26%) and 8 patients (23%), respectively. The EVR rate improved to 43%, ETVR to 49% and SVR to 57% when a HBV DNA cutoff level of <20,000 copies/mL was used. Pretreatment HBsAg level was not a predictor for SVR on univariate analysis, but correlated with decline in HBV DNA levels at week 48 and 72. On multivariate logistic regression analysis, low body weight, high ALT, low HBV DNA and low triglyceride levels were identified as baseline predictors of SVR.

Conclusion: HBeAg-negative genotype D naïve patients treated with PEG-INF α-2a achieved SVR in 23% (HBV<400 copies/mL) and 57% (HBV <20,000 copies/mL) of patients, a better response than previously reported that might be related to the absence of drug resistance in these naïve patients. Pretreatment predictors of SVR were low body weight, high ALT, low HBV DNA and low triglycerides.

Project title

Interferon-γ-Inducible Protein 10 (IP-10) Predicts Viral Response in Various Heterogeneity of Chronic Hepatitis-C Genotype 4.

Investigators: Hamad Al Ashgar, MD, Mohamed Q. Khan, MRCP (UK), Ahmed Al Qahtani, PhD.

Project description

Background: High systemic levels of IP-10 at the onset of combination therapy for chronic hepatitis-C predict poor outcome but details regarding the impact of pretreatment IP-10 levels as predictor of response in various genetic heterogeneity of HCV-4 remain unknown.

Aims: To analyze the incidence and treatment outcome of HCV-4 sub-genotypes and correlate their response to combination therapy with pre-treatment IP-10 levels.

Methods: Stored plasma from 64 HCV-4 patients, who received combination therapy were retrieved. Their baseline IP-10 levels and sub-genotypes were measured and correlated with their treatment responses.

Results: Prevalence of HCV-4 sub-genotypes were 4a=48.4%(31/64), 4d=39%(25/64), 4n=6.25%(4/64), and remaining (4m,4l,4r,4o) combined 6.25%(4/64). SVR in all HCV-4 patients was 64% (41/64) but when analyzed in each sub-genotypes, then 4a was 77.4% (24/31), 4d 52% (13/25) and combined 62.5% (5/8, p=0.046). Non-responders had significantly higher baseline IP-10 levels (840.1±490.6pg/mL) compared with responders (462.4±282.7pg/mL, p<0.002). Pretreatment IP-10 in genotype-4a, 4d and combined sub-genotype were not statistically significant (p=0.904). The baseline IP-10 among sub-genotypes in responders and non-responders were as followed, 4a 92.2±240.1pg/mL and 830.7±458.3pg/mL respectively (p<0.102), 4d 366.5±267.6pg/mL and 889.6±502.2pg/mL (p<0.005) and combined genotypes 568.5±472.7pg/mL and 663.4±669.7pg/mL (p=0.842). In genotype 4, baseline IP-10 levels greater than 359 pg/mL identified 82% of non-responders and lower than 359 pg/mL identified 45% of responders.

Conclusion: 4a and 4d were the commonest sub-genotypes, where 4a responded significantly better than 4d. Baseline IP-10 level was significantly lower in responders but when analyzed in various sub-genotypes, then 4d patients had significantly lower IP-10 levels than 4a, suggest a predictor of response.

THE DEPARTMENT OF

Nursing Affairs

Nursing Affairs

Director or Nursing Practice and Research

Gillian Ingram RN, BN, MN

Nursing Affairs is committed to conducting high-quality research that informs nursing practice at KFSH&RC. Nurses are encouraged to develop research proposals, conduct research in teams and to disseminate research findings. Nursing Affairs provides several support structures for nurses in order to facilitate involvement in research including the Nursing Research Council and a Nursing Research Mentorship Program. Supporting nurses in their quest for new knowledge plays an important role in the professional development of individual nurses and the nursing profession. Nursing Affairs is committed to expanding our research program and have recently recruited two nursing clinical trial coordinators who will play an integral role in expanding the nursing research profile in 2011. Nursing Affairs continually pursues the translation of high quality research into nursing practice which is paramount to improving patient care delivery.

RAC APPROVED RESEARCH ACTIVITY

Project title

Use of Double Lumen Central Venous Catheters for the Drainage of Pleural Effusion in Pediatrics: A Prospective Observational Pilot Study. RAC # 2101 072.

Investigators: N. Shwaihet and G. Ingram.

Project description

This prospective observational study came about due to the placement of double lumen central venous catheters for pleural drainage in pediatrics post cardiac surgery. The literature was not available to draw any conclusions regarding the safety or efficiencies of such devices. The investigators designed this study to measure the safety and efficiency of central venous catheters for pleural drainage in pediatrics with the purpose of informing patient care decision making at the bedside.

Progress

This study is currently in the data collection phase and to date has recruited 20 subjects in five months. Data collection is planned to go on for a total of six months.

Project title

Humidified oxygen versus air for the treatment of Chemotherapy/ Radiationtherapy induced mucositis. RAC # 2101 084.

Investigators: G. Ingram, A. Amro, L. McGregor, J. Ordonio, W. Peterson, C. Rodriguez.

Project Description

Oncology induced mucositis is a painfully, debilitating side effect for patients undergoing chemotherapy/ radiotherapy. Motivated by a striking clinical observation, in which nurses saw remarkable healing of mouth ulcers in one patient receiving humidified oxygen, the investigators of this study have designed a triple arm, randomized control trial to determine the effectiveness of humidified air versus oxygen in the treatment of oral mucositis.

Progress

This project was recently approved by the RAC. Commencement of the study and recruitment of participants is imminent.

Project title

Nursing education and the impact on patient outcomes: A Randomized Control Trial. RAC # 2101 063.

Investigators: V. Farquhar, G. Ingram, B. Foreman.

Project description

Nursing education departments are constantly under scrutiny when resources in patient care organizations are tight. This randomized control trial was designed by the researchers to expand the evaluation of nursing education in an acute care hospital setting. In this study nursing education is being evaluated on four levels based on Kirkpatrick's assessment hierarchy incorporating basic evaluation of the education program right through to the impact on patient outcomes.

Progress

This study is well underway having completed three sets of data collection. Six month post-intervention data collection is due to take place in May 2011.

Project title

Risk Factors for Surgical Site Infection in Colorectal Surgery in Saudi Arabia. RAC # 2041071.

Investigators: D. Hibbert, N. Al-Sanea, A. Abdul Jabbar, N. Elkum.

Project description

This prospective observational trial was designed to evaluate risk factors for surgical site infection in colorectal surgery in Saudi Arabia.

Progress

Data analysis in currently underway.

THE DEPARTMENT OF

Pathology and Laboratory Medicine

The Department of Pathology and Laboratory Medicine

Chairman
Maher Albitar, MD

Project title

Evaluation of a new D-Dimer test in combination with preset clinical probability score for diagnosis of pulmonary embolism and deep venous thrombosis, RAC # 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 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 pretest 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 scores system and D-Dimer in patients presenting with DVT/PE.

Progress, major findings

Currently, the project has 171 patients and planning to reach 200 patients. Analyze data.

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 # 2091 056

Investigators: TM Owaidah, A Al Shaikh, M Abdulaali, R Al-Nounou

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, major findings

Collected 50 data, initial analysis done and abstract was submitted.

Project title

The significant of Phosphatidylserine as Predictor of Antiphospholipid Syndrome and Concordance with other Antiphospholipid Antibodies, RAC # 2091 039

Investigators: TM Owaidah, O Khoja, M Al Kaff, T Al Shehri, H Khogeer

Project description

Antiphospholipid 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 new APA that can be used as marker for APS.

Progress, major findings

Accumulated 200 patients and planning to reach 300 patients. Data analysis.

Project title

Molecular genetics for glanzmann thrombasthenia at KFSH-RC, RAC # 2091 067

Investigators: H. Masmali, TM Owaidah, A Albanyan, A Almusa, M Saleh, A Al Jefri, H AlZahrani, R Al-Nounou, R Nasr M Abou-Riash, H Abalkhail

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, major findings

36 patients have been requested and tested. More patients to be requested and to read.

Project title

Prevalence of Bleeding disorders among adolescents in Riyadh City , RAC # 2111 008

Investigators: TM Owaidah, H Al Zahrani, A Al-Zahrani, M Al Medani

Project description

This is an epidemiological prospective study to detect bleeding disorders among adolescences. It is a questionnaire base study and will be conducted by interviewers; samples will be collected to confirm suspected cases. This study will be conducted in collaboration with Ministry of Education.

The estimated number of samples will be around 2,198 patients of a period of 18 months and to detect around 200 cases.

Progress, major findings

Under evaluation for KACST funding

Project title

Screening for prevalence and incidence of Hemophilia A & B Inhibitors among hemophilic patient, RAC # 2081 077

Investigators: 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, H Abalkhail

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 inhibitor formation in both types of hemphilia 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.

Progress, major findings

Accumulated 200 patients and plan to reach 500 patients in 2 years more. Data analysis.

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).

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, randomized, open-label clinical trial on inhibitor frequency in patients previously untreated (PUPs) or minimally blood component-treated (MBCTPs) when exposed to plasma-derived, won Willebrand factor-containing factor VIII (VWF/FVIII) concentrates or to recombinant factor VIIII (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, major findings

Collected one (1) patient and 1 more year for accrual up to 10 patients and the follow-up for 2 yrs

Project title

A Prospective Observational Study on the Use of NovoSeven (Activated Recombinant Human Factor VIIa) for on Demand

Treatment of Mild to Moderate Bleeds in Haemophilia A and B Patients with Inhibitors, RAC # 2091 019

Investigators: M. Saleh, H. Al Zahrani, TM Owaidah

Project description

Prospective

Progress, major findings

To start accumulation of patients this year

Project title

National Screening program for Genetics mutations causing familial Hyoercholesterolemia among Saudi Arabia Population; and the Development of a Molecular Diagnostic Testing, RAC # 2090019

Investigators: Faisal Al-allaf, Halah Abalkhail, Abdullah Al-Ashwal

Project description

Familial hypercholesterolemia (FH) is hereditary in an autosomal dominant manner and is a major risk factor for the development of CHD. Approximately, half of the heterozygous men with familial hypercholesterolaemia, if untreated, will have developed clinically evident CHD by the age of 55 years. Affected heterozygous women from the same families typically develop CHD about 9 years later than their affected male relatives. We aim to collect samples from 100 families from several Saudi regions suspected FH and Identify the causative mutation in LDLR and Apolipoprotein B and PCSK9 genes.

Progress

We have collected 45 cases known to have Familial Hypercholestrolemia, DNA is extracted and saved at the Molecular Genetics. Mutation analysis will be performed.

Project title

Genomics and transcriptomics analysis of ovarian hyperstimulation syndrome: An integrated molecular look to a complex syndromeRAC#: 2100002

Investigators: Maha Dagestani, Serdar Coskun, Mashael Al Deery, Dilek Colak, Khalid A. Awartani, Namik Kaya

Project description

Ovarian hyperstimulation syndrome (OHSS) usually is an iatrogenic exaggerated response and could be a potentially life-threatening during ovarian stimulation treatments. The pathogenesis of the syndrome is not well-studied at the molecular level. In this project, we are focusing on two target sites, blood and ovary to study OHSS. Our approach includes genome-wide gene expression profiling of the different stages of OHSS, genome-wide association analysis to find potentially important SNPs and Copy Number Variations (CNVs) causing susceptibility as risk factors.

Progress

This project is approved in 2010 and the work is ongoing. The project is given 2 million SR grant from KACST through King Saud University.

Project title

Preimplantation genetic diagnosis by haplotyping (PGH) using whole genome amplification, RAC # 2081061

Investigators: Qubbaj, W., Awartani, K., Al-Rejjal, R., Al-Hassan, S., Al-Deery M., Coskun, S., Al-Owain, M., Al-Sayed, M., Al-Hassnan, Z., Banjar, H., Bal-Obaid, A., Qari, A., Rahbeeni, Z.

Project description

Preimplantation Genetic Diagnosis (PGD) is an effective reproductive option applied to couples at risk of having a pregnancy affected with a known genetic disease. The number of diseases that PGD was effectively used is in hundreds now. In the application of PGD, one of the limiting factors is the necessity to identify the genes and the mutations that cause the disease. In the absence of any identified mutations in an inherited disease, PGD cannot be offered which disqualifies number of patients who can otherwise benefit from PGD.

Preimplantation genetic haplotyping (PGH) following multiple displacement amplification (MDA) of single blastomer is the testing for multiple markers (STRs) linked to the target gene causing the disease. Knowing the parental haplotypes associated with the mutated and the normal alleles enables the identification of out coming haplotypes in the MDA products and predicting the diagnosis. PGH offers several advantages to the direct mutation testing, since the finding of the mutation within the gene of interest is often difficult, it is labor-intensive, time-consuming and a costly process. PGH allows the haplotype associated with the mutated allele to be identified.

Aim of the study is to develop a new testing methodology for preimplantation genetic diagnosis. PGH will be established

on two levels: *(i)* in patients with known mutation in parallel to mutation testing, *(ii)* and in patients, were the gene causing the disease and its inheritance pattern is known; but mutation is not identified.

Progress

This study was approved in 2008 and the study is ongoing. The target number of patients is reached for level 1. For the level 2, more patients are needed.

Project title

Obstetrical and neonatal outcome after PGD: Eight years of experience at KFHRC, RAC # 2101013

Investigators: Elham Al Mardawi, Samar Toukhi, Serdar Coskun, Wafa Qubbaj, Maha Tulbah, Wesam Kurdi.

Project description

The objectives were to determine if there is any observable effect of preimplantation genetic diagnosis (PGD) on obstetrical outcome and perinatal morbidity and mortality, birth defects, neonatal outcome in adition finding the rate of misdiagnosis.

Progress

A retrospective chart review of PGD patients from Jan 2001- Dec 2009 was conducted. A total of 70 PGD pregnancies and 70 matching spontaneously conceived pregnancies were reviewed. Data were collected from 79 children born after PGD and compared to 72 children born after spontaneous pregnancies. PGD group had significantly more multiple pregnancies. However, there was no statistically significant difference between other outcomes in terms of: birth weight, GA at delivery, perinatal mortality and presence of congenital malformations. The misdiagnosis rate was 1.4%.

Project title

Whole genome amplification of single cells using different amplification trategies. RAC#: 209 0013

Investigators: Serdar Coskun, Wafa Qubbaj

Project description

Preimplantation genetic diagnosis (PGD) is an early form of prenatal diagnosis and utilizes the genetic diagnosis of a single cell biopsied from an embryo. The low quantity DNA in a single cell presents a number of complications including contamination, amplification failure, and preferential amplification or allele dropout (ADO) in heterozygous loci. Whole genome amplification (WGA) is a technique to specifically increase the DNA quantities that are originating from samples with limited DNA contents. The application of such techniques would greatly enhance our maneuverability when the starting genetic material is derived from just a single cell. There are two recent powerful WGA methods became available through commercial kits, namely multiple displacement amplification (MDA) and GenomePlex technology. Both methods have already been utilized in PGD and compared for genome coverage in genomic DNA. There is no study to compare these two techniques in single cells. 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.

Progress

This project was approved in 2009. The experiment for MDA with RepliG kit was performed, others were not studied due to personnel shortage and a similar study was published at the end of 2010. The study will be closed.

Project title

Cell free fetal DNA (cffDNA) in maternal circulation: An alternative approach for non-invasive prenatal diagnosis. RAC # 209 1001

Investigators: Qubbaj W., Coskun S., Al-Hassnan Z., Al-Hassan S., Barakas B.

Project description

This study was approved in 2009 and not progressed due to personnel shortage. We submitted this proposal to National Comprehensive Plan for Science and Technology grant program for funding.

Project title

A Multi-Centre Evaluation of the Immune Response of the 13-valent Pneumococcal Conjugate Vaccine in children with Sickle Cell Disease, RAC # 2101 036

Investigators: Sami Al-Hajjar, Ebrahim Bin Hussein, Sahar Al Thawadi, Abdulla Al-Jarfi, Rana Tawfiq

Progress, major findings

Data collection in progress

Project title

2009 H1N1 Influenza Experience in A Tertiary Care Hospital in Saudi Arabia, RAC # 2101 010

Investigators: Wafeeq Ahmed Mahmood, Sahar Al-Thawadi, Nada Al Qadheeb, Ibrahim Al-Sanouri

Project description

To describe the demographic, epidemiological, clinical characteristics, treatment and outcomes of adult patients with H1N1 Influenza infection admitted to King Faisal Specialist Hospital & Research Center (KFSHRC) in Riyadh, Saudi Arabia

Progress, major findings

Data has been gathered, analysis in progress

Project title

Isolation and Clinical Significance of Nontuberculous Mycobacteria, RAC # 2101 055

Investigators: Sahar Althawadi, Abdulrahman A. Alrajhi, Suliman Al Jumaah, Abdullah Al-Mobeireek, Saud Al-Mukhaini, Mohannad Abu-Rageila, Manal Jaber AlHaj, Edwin Atienza

Project description

To describe the clinical significance of nontuberculous mycobacteria isolates in KFSH population

Progress, major findings

Data collection in progress

Project title

Clostridium Difficile-Associated Disease at KFSH&RC Critical Care and General Floors, RAC # 2101 018

Investigators: Nojoud Alkhaldi, Magid Halim, Sahar Al-Thawadi

Project description

To examine and review the incidence of healthcare associated clostridium difficile in KFSH and evaluate the emphasis on patient outcome.

Progress, major findings

Data collection in progress

THE DEPARTMENT OF

Surgery

The Department of Surgery

Chairman
Dieter C. Broering, MD., Ph.D., FEBS

Deputy Chairman
Ashour Mahmoud, MBBCh, FRCS, FEBTCS

The Department of Surgery is dedicated to the best patient care, teaching and research.

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.

During the Year 2010, The Department of Surgery has continued to perform its variety of activities to provide best patient care, which constitute Research Projects, and many educational activities through workshops, International Forums, Animal Lab workshops and Microsurgery training sessions.

In order to promote research awareness and activities, the Department is conducting its Annual Surgical Research Day, which was started in 2001, wherein junior staff and new generation of Surgeons are exposed to the research environment from the beginning of their career so they can carry it over during their training, post training period, and during their practice as senior staff.

Other members of the staff are also encouraged to conduct clinical trials, studies, and research projects either individually or in collaboration with other departments.

At the end of 2010, the department had 13 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.

RESEARCH PROJECTS

Project title

Prognostic Significance of Genetic Alterations in Saudi Colorectal Cancers, RAC # 2080 030,KACST Project #: 08-MED479-20

Principal Investigator: Khawla Al-Kuraya, MD, FCAP

Co-Investigators: Shahab Uddin Khan, PhD, Maqbool Ahmed, Abdul Khalid Siraj, PhD, Zeenath Jehan, PhD, Rong Bu, MD, PhD, Jehad Abubaker, PhD

Project description

Although chromosomal instability pathway and microsatellite instability in colorectal carcinomas (CRC) has been extensively researched in the West, there is a dearth of literature documenting these genetic abnormalities in the Saudi CRC. Recently, we have studied the genomic instability pathways in Saudi CRC and subsequently reported the incidence of PIK3CA mutation and PTEN protein expression in Middle Eastern CRCs. Phosphatidylinositol 3'-kinase (PI3K)/AKT and MAPK pathways are two of the key signaling pathways regulating cell proliferation, differentiation, senescence and apoptosis. Earlier studies have suggested possible relationship between both RAS/RAF/MEK and PI3K/AKT pathways. We will investigate the role of PI3K/AKT, MAPK signaling pathways and EGFR dysregulations in CRC using a large tissue microarray cohort of tumor samples. The studies of specific aim 1 determine the prognostic significance of genetic mutations related to MAPK kinase pathway such as KRAS and BRAF mutations and their potential cross talk with other genetic alterations in PI3K/AKT pathway. The studies of aim 2 will determine the prognostic significance of EGFR alterations in Saudi CRC cases. The studies of aim 3 will investigate the prognostic values of micro RNAs: mir-7, mir-21, and miR-214 in Saudi CRCs.

This project should provide comprehensive view of the clinical implications of different genetic alterations operating in the PI3K/AKT and RAS/RAF/MEK pathways and add to our understanding about the roles by which these genetic alterations influence Saudi CRC tumorigenesis and patient outcome.

Collaborators: Nasser Al-Sanea, MD, Colorectal Unit, Department of Surgery, Fouad Al-Dayel, MD, Department of Pathology

Progress

On-going.

Project title

Persistent Hyperinsulinemic Hypoglycemia of Infancy (Nesidioblastosis): Pathological Stratification, RAC Proposal # 2071-010

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

On-going

Project title

Wilm's Tumor and Breast Feeding, RAC Proposal #: 2071-004

Principal Investigator: Dr. Saud Al-Shanafey

Co-Principal Investigator: Fawaz Ibrahim, Salman Taghreed

Project description

To check if there is any relation between breast feeding & Wilm's tumor.

Progress

On-going.

Project title

Renal Tumors in Infants, RAC Proposal #: 2071-009

Principal Investigator: Dr. Saud Al-Shanafey

Co-Principal Investigator: Fawaz Ibrahim

Project description

Simple review of renal tumors in infants, descriptive study.

Progress

On-going.

Project title

External Pressure Compression for Umbilical Hernia Management in Infants: Randomized Clinical Trial, RAC Proposal #: 2071-070

Principal Investigator: Dr. Saud Al-Shanafey

Co-Principal Investigator: 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

On-going.

Project title

Laparoscopic liver biopsy, RAC Proposal #: RAC#2101022

Principal Investigator: Zakaria Habib

Co-Principal Investigator: Mila Kolar, Mohammed Banemai Tabasum Akram, Hadeel Al Mana

Project description

Liver biopsy is used frequently in different specialties of pediatrics in order to reach a diagnosis and assess the extent of liver disease and response to medical therapy. Liver biopsy can be obtained by a gastroenterologist, radiologist or a surgeon. The aim of the study is to assess the safety of laparoscopic liver biopsy and to assess the diagnostic yield of laparoscopic liver biopsy.

Progress

Submitted to ORA for approval.

Project title

Clinical and Audiological Outcome of Myringotomy Tubes Insertion on Cleft Lip & Palate Patients, RAC Proposal #: 2010-069

Principal Investigator: Dr. Ali Malaq, Dr. Atif Rafique, Gheid Abuharb, Clinical Audiologist

Co-Principal Investigator: Hanan Al Gammas, Clinical Research Coordinator

Project description

The patient with cleft lip and palate are known to have middle ear problems, because of the abnormal function of the Eustachian tubes.

So these patients during the palate repair are referred to ENT and myringotomy tubes are inserted. Our study aimed to evacuta whether inseting tubes in early have positive impact on the hearing.

Progress

On-going.

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 Proposal #: 2081-021

Principal Investigator: Dr. Nahar Al Anezi, Dr. Adra, 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

On-going.

Project title

Phase II prospective study of the Clinical Efficacy of Autologous Stem Cell Transplantation in patients with Critical Limb Ischemia, RAC Proposal #: 2081-026

Principal Investigator: Dr. Saad AlGarni

Co-Principal Investigator: Dr. Shaltout, Mohamed

Project description

This study is testing the efficacy of stem cell therapy in the treatment of patients with significant peripheral vascular disease who has no choice except amputation or to live with severe rest pain. The idea of this stem cell therapy is to improve angiogenesis, ie new collateral to carry blood from the proximal arteries to distal diseased limb.

Progress

On-going.

Project title

Saudi Optical Coherence Tomography for Saudi Diabetic Macular Edema Study, RAC Proposal #: 2091-011

Principal Investigator: Dr. Selwa Al Hazzaa

Co-Principal Investigator: Dr. Faisal Al Qahtani, Dr. Amal Al Hemidan

Project description

To compare DME in Saudi population at KFSH with the American population at JHH.

Progress

On-going.

Project title

Genetics of Vision Impairment in Saudi Arabia., RAC Proposal #: 2070023

Principal Investigator: Dr. Fawzan Al Kuraya

Co-Principal Investigator: Dr. Selwa Al Hazzaa

Project description

Vision loss (blindness and vision impairment included) is an important disabling condition among Saudis with significant medical, economic and social impact. Genetically determined conditions contribute significantly to the pool of vision loss in the Kingdom particularly among children where their frequency approaches 70%. This usually high frequency is the result of several factors the most common important of which is the high frequency of autosomal recessive disorder (many of which will inevitably involve the complex organ of the eye) as a result of high degree of inbreeding and consanguinity. Our research group has an extensive experience in mapping mendelian disorders, including genetic eye conditions. Similarly, we have solid experience in clinical, molecular and developmental genetics. We propose to focus our existing expertise in Saudi Arabia. Characterization these mutations will have an obvious impact on the medical care of the affected individuals since it makes prenatal/preimplantation diagnosis available options but it also represents a step in the right direstion to this approach. In addition, our group has a keen interest in understanding how different mutations affect the protein function of the respective genes. Furthermore, new genes identified in the course of this work represent an exciting opportunity to better understand the molecular mechanisms that govern human eye formation by studying their expression pattern and protein function. Given the scope of this project, the methodology will not only include linkage analysis but will also use the latest available tools in developmental and molecular genetics. This is a five year project that will recruit and study any eye condition that is likely to have a genetic underlying defect. Eye disorders the underlying genetic lesion of which is known will also be included since the spectrum of mutations among Saudi could, and in fact has been shown in many instances to, be different.

Progress

On-going.

Project title

Characterization of the Molecular Basis of Hereditary Deafness in the Saudi Population, RAC Proposal #: 2080084

Principal Investigator: Imtiaz F

Co-Principal Investigator: Al-Hazzaa SAF. Taibah K, Ramzan K, Al-Owain M, Bin Khamis G,

Project description

Recessively inherited diseases are more prevalent in population where consanguineous marriages are common, like Saudi Arabia. Deafness is the most common sensory deficit in humans (1: 1000 child births) with both genetic (50%) etiologies. Our study hopes to define the genetics of non-syndromic and syndromic deafness in this population. Families with profound congenital deafness and an autosomal recessive mode of inheritance are a powerful resource for genetic linkage studies of recessively inherited deafness. The most common forms of hereditary deafness, their incidence and distribution in the Saudi population will be identified as the result from the study. The benefit of this study is also to provide knowledge and awareness through screening of carrier status and genetic counseling, therapy will have a major impact upon early intervention for and prevention of hereditary deafness.

Progress

On-going.

Project title

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multinational Clinical Study to evaluate the Efficacy and Safety of 2.0 mg/kg/week and 2.0mg/kg/every other week BMN 110 in patients with Mucopolysaccharidosis IVA (Morquio A Syndrome). (Protocol Number: MOR-004, IND: BMN 110, EudraCT number: 2010-0210198-18), RAC Proposal #: Protocol Number: MOR-004, IND: BMN 110, EudraCT number: 2010-0210198-18)

Principal Investigator: M. Al Sayed

Co-Principal Investigator: N. Awada, R Moslmani, L Al-Otaibi, S. Al Hazzaa

Project description

Mucopolysaccharidosis IVA (Morquio A syndrome, MPS IVA) is an inherited autosomal recessive disorder characterized by deficient activity of N-acetylgalactosamine-6-sulfatase (GALNS), resulting in macroscopic accumulation of the glycosaminoglycan (GAG) keratan sulfate (KS) in tissue macrophages, hyaline cartilage and other connective tissues, heart valve, and cornea as well as excretion in the urine. This accumulation causes multiple clinical manifestations including impaired functional capacity, endurance, and quality of life. There is currently no standard accepted treatment for MPS IVA other than supportive care. Enzyme replacement therapy with BMN 110 (rhGALNS) may be a potential new treatment option for MPS IVA patients. BMN 110 is expected to reduce the progressive accumulation of KS and improve signs and symptoms of the disease.

Progress

Submitted to ORA for approval.

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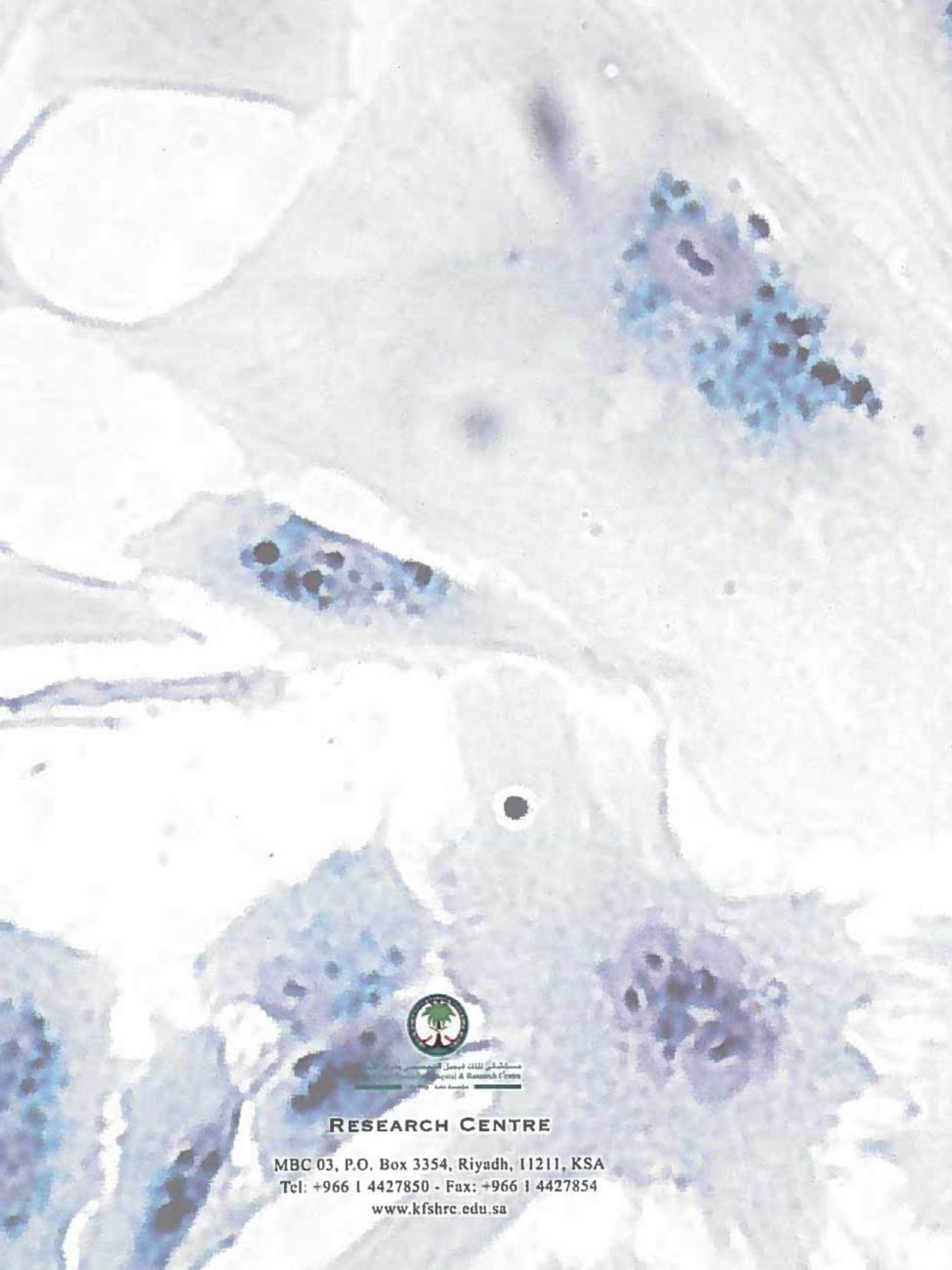

RESEARCH CENTRE

MBC 03, P.O. Box 3354, Riyadh, 11211, KSA
Tel: +966 1 4427850 - Fax: +966 1 4427854
www.kfshrc.edu.sa